UPBEAT

the relationship between maternal obesity and cardiometabolic outcomes in preschool children

Dalrymple, Katie

Awarding institution:
King's College London

UPBEAT: The relationship between maternal obesity and cardiometabolic outcomes in preschool children

Kathryn Vere Dalrymple

A thesis submitted to King's College London for the degree of Doctor of Philosophy

Department of Women and Children's Health

King's College London

February 2020

Table of Contents

Table of Figures

Table of Tables

Acknowledgements

I would like to thank my supervisors, Professor Lucilla Poston and Dr Majella O'Keeffe, who have supported me throughout my PhD training. They are inspiring researchers from whom I have learnt so much. Lucilla especially has been a wonderful mentor and has given me a fantastic foundation in research, built on collaboration, a drive to ask questions and to strive to always want the best out of your research.

My thanks also go to all the research members, past and present, from the UPBEAT team. To Paul, Florence and Shahina for introducing me to statistics and showing me how to enjoy data analysis. To colleagues in the department and in research room 2, for your good humour, coffee and constant supply of cake and biscuits. A special mention to Angela, you have been a great friend throughout the time we have known each other, and I look forward to working with you for many years to come.

I would like to acknowledge the participants from the UPBEAT study who have provided data for this research. Thank you to the British Heart Foundation for funding my PhD and the NIHR, MRC UK, CSO (Scotland) BRC (Guy's and St Thomas'), Tommy's charity and the EarlyNutrition Project for their generous funding for the UPBEAT study. To the UPBEAT collaborators at the University of Bristol and the University of Southampton, especially Professor Keith Godfrey, who has always been so encouraging of the work we do in the Department of Women and Children's Health.

On a personal note, thank you to my family and close friends, especially to Joe for his patience, encouragement and continued faith in my ability over the last few years, for which I am extremely grateful.

Abbreviations

ALSPAC: Avon Longitudinal study of Parents and Children

ANS: Autonomic nervous system

ASQ: Age's and Stages of Development

BIA: Bioelectric Impedance Assay

BISQ: Brief-Infant Sleep Questionnaire

BMI: Body mass index

CEBQ: Children's Eating Behaviour Questionnaire

CHOP: The EU Childhood Obesity Programme

CI: Confidence interval

DXA: Dual energy x-ray absorptiometry

DoHaD: Developmental Origins of health and Disease

ECHO: Ending CHildhood Obesity

EPDS: Edinburgh Postnatal Depression Scale

EPIC: European Prospective Investigation of Cancer

FFQ: Food frequency questionnaire

GDM: Gestational Diabetes Mellitus

GI: Glycaemic index

GL: Glycaemic load

GWG: Gestational weight gain

HAPO: Hyperglycaemia and Adverse Pregnancy Outcome

IMD: Index of multiple deprivation

IADPSG: International Association of the Diabetes and Pregnancy Study Group

IOTF: International Obesity Task Force

IOM: Institute of Medicine

IPAQ: International physical activity questionnaire

IPD: Individual participant data

IPDMA: Individual participant data meta-analysis

i-WIP: International Weight in Pregnancy

LDL: Low density lipoprotein

LGA: Large for gestational age

LiP: Lifestyle in Pregnancy

LSOA: Lower super output area

METs: Metabolic equivalent task

NAM: National Academy for Medicine

OR: Odds ratio

PEAPOD: Air-displacement plethysmography

PlGF: Placental growth factor

PROBIT: Promotion of Breasting Intervention Trial

RCT: randomised controlled trial

SD: Standard deviation

SCOPE: SCreening fOr Pregnancy Endpoint

SWS: Southampton Women's Survey

SDQ: Strengths and Difficulties Questionnaire

SFA: Saturated fatty acids

VLDL: Very low-density lipoprotein

WHO: World Health Organisation

UK: United Kingdom

UPBEAT: UK Pregnancy Better Eating and Activity Trial

Statement of contribution

All aspects of the UPBEAT trial were designed by the principal and co-investigators, listed alongside all UPBEAT contributors in the supplementary materials published with the final study paper (Poston et al., 2015).

This thesis uses data collected from the main UPBEAT trial and the 3-year follow-up of UPBEAT. All data was collected by research midwives/assistants at the eight trial sites, between July 2009 and October 2017, under the supervision of Dr Annette Briley and Claire Singh. I started at St Thomas' hospital in October 2016 and for the final year of data collection for the 3-year follow-up I observed the UPBEAT visits which took place at St Thomas' hospital. During this year I monitored the participant reported questionnaires on the database for abnormal responses and if appropriate generated queries with the research team to verify the data.

Once the 3-year follow-up ended in October 2017, I formulated and completed all statistical analyses under the guidance of my supervisors, Professor Lucilla Poston and Dr Majella O'Keeffe. I was responsible for all data management, statistical analysis and interpretation of finding throughout the course of the PhD, with statistical guidance from Mr Paul Seed, Shahina Begum and Florence Tydeman. For the metabolome analysis in chapter 4 Dr Harriet Mills provided the raw data and Professor Deborah Lawlor and Dr Harriet Mills advised on the data analysis plan. Additional statistical and epidemiological support was provided by Professor Keith Godfrey. Dr Angela Flynn provided advice for the nutritional analyses presented in this thesis.

I wrote the protocol and conducted the systematic review (Chapter 3) with Julia Martyni-Orenowicz as a second reviewer. I wrote the manuscripts presented in Chapters 3 and 5 and edited in response to co-authors comments. Chapters 3 and 5 are presented in the final submitted format to the journals and the published versions are in the final section of this thesis. Chapter 4 has been submitted for publication and is in the current format.

Presentations and publications arising from this work

Publications:

Dalrymple K, Tydeman F, Flynn A et al. Adiposity and cardiovascular outcomes in 3-year-old children of participants in UPBEAT, a complex intervention in pregnant women with obesity. *Pediatric Obesity*. Submitted

Flynn A, Thompson J, **Dalrymple K** et al. Childhood dietary patterns and body composition at age 6 years: The Children of SCOPE study. *BJN*. Accepted.

Dalrymple K, Flynn A and Seed P et al. Associations between dietary patterns, eating behaviours and body composition and adiposity in 3-year old children of mothers with obesity. *Pediatric Obesity*. 2020.

Bland C, **Dalrymple K** and White S et al. Smartphone applications available to pregnant women in the United Kingdom: An assessment of nutritional information. *Matern Child Nutr.* 2019.

Dalrymple K, Thompson J and Begum S et al. Relationships of Maternal Body Mass Index and Plasma Biomarkers with Childhood Body Mass Index and Adiposity at 6 years; the Children of SCOPE study. *Pediatric Obesity*. 2019, 14(10): e12537

Dalrymple K, Flynn A and Relph S et al. Lifestyle Interventions in Overweight and Obese Pregnant or Postpartum Women for Postpartum Weight Management: A Systematic Review of the Literature. *Nutrients*. 2018, *10*, 1704.

Patel N*, **Dalrymple K*** et al. Mode of infant feeding, eating behaviour and anthropometry in infants at 6-months of age born to obese women - A secondary analysis of the UPBEAT Trial. *BMC Preg & Child*. 2018, 18(1):35

Flynn A, Begum S and **Dalrymple K** et al. Relationships between Maternal Obesity and Maternal and Neonatal Iron Status. *Nutrients.* 2018, 10 (8): 1000

Dalrymple K, Martyni-Orenowicz J and Flynn A et al. Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature. *Matern Child Nutr*. 2018. 14(4): e12628

Flynn A*, **Dalrymple K*** et al. Dietary interventions in overweight and obese pregnant women: a systematic review of the content, delivery, and outcomes of randomized controlled trials. *Nutr Rev.* 2016. 74 (5): 312-328

Oral Presentations:

Developmental Origins of Health and Disease (DoHaD): Rotterdam October 2017**:** Oral Presentation: Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature.

Society of Reproductive Investigation (SRI): Paris March 2019**:** Oral Presentation: Childhood adiposity and cardiovascular outcomes at 3 years following a randomised controlled trial of a behavioural intervention in obese pregnant women (the UPBEAT Trial).

European Nutrition Conference (FENs): Dublin, October 2019: Oral Presentation: 'Analysis of antenatal and postnatal determinants which promote postpartum weight loss in obese women - An analysis from the UPBEAT trial.
Recipient of a Nutrition Society Travel Award

Poster Presentations:

Nutrition Society Conference: London July 2017**:** Poster Presentation: Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature.
Recipient of The Best Student Presentation

SRI: San Diego March 2018**:** Poster Presentation: The effects of feeding practices and appetitive traits on infant anthropometry in 6-month infants born to obese women - a secondary analysis of the UPBEAT trial.
Recipient of the Young Investigators Travel Award

Nutrition Society Conference: Leeds, July 2018: Poster Presentation: Preventing postpartum weight retention: Lifestyle interventions in pregnancy, postpartum or both. A systematic review of the literature.
Recipient of The Best Student Presentation

British Heart Foundation Conference: Cambridge September 2019**:** Poster Presentation: Childhood adiposity and cardiovascular outcomes at 3 years following a randomised controlled trial of a behavioural intervention in obese pregnant women (the UPBEAT Trial).

DoHaD: Melbourne October 2019**:** Poster Presentations: (1) Relationships between maternal body mass index and plasma biomarkers with childhood body mass index and adiposity at 6 years; the Children of SCOPE Study (2) Potentially modifiable determinants of obesity and adiposity in children of obese mothers.

Abstract

Background: In parallel with the global obesity epidemic, rates of maternal obesity are increasing worldwide, with significant consequences for both the mother and her child. Acutely, the mother is at risk of gestational diabetes and adverse outcomes in labour associated with fetal macrosomia. In the longer-term obesity in pregnancy is associated with type 2 diabetes and cardiovascular disease. Children of women with obesity are at greater risk of developing obesity and cardiometabolic dysfunction themselves and these conditions track across the life course. Effective strategies to stem the rising trend of childhood obesity are needed and pregnancy represents an opportune window to intervene.

Methods: In the UK Pregnancy Better Eating and Activity Trial (UPBEAT), pregnant women with obesity were randomised to a dietary and physical activity intervention or standard antenatal care in early pregnancy. For this thesis, a systematic review of maternal lifestyle interventions and childhood obesity was undertaken. The thesis then addressed the hypothesis that the UPBEAT antenatal intervention would reduce the risk of obesity and cardiovascular disorders in the children at three years of age. Further analyses explored the longer-term impact of the intervention on maternal lifestyle, and the determinants of obesity in the children.

Results: The UPBEAT intervention was not associated with improved offspring body composition at 3-years of age. However, it was associated with a reduction in the children's resting pulse rate. A sustained improvement in maternal dietary intake was also evident in women randomised to the intervention arm. Analysis of the UPBEAT data as a cohort identified that lower gestational weight gain, breastfeeding, a healthier dietary intake in the child, and lower appetite responses were associated with lower measures of childhood obesity.

Conclusion: To summarise, an antenatal lifestyle intervention in women with obesity was found to improve offspring cardiovascular health. Modifiable antenatal and postnatal determinants related to improved childhood body composition were also identified. These observations could inform future public health strategies for obesity prevention in pre-school children.

Foreword

Obesity is a complex multifactorial disease with co-morbidities including cardiovascular and metabolic dysfunction (Martin-Rodriguez et al., 2015). The current global epidemic presents a major challenge for public health across the life course. Irrespective of gender, ethnicity, socioeconomic status or country of residence (Roberto et al., 2015) worldwide prevalence continues to increase (Blüher, 2019). Since the determinants of obesity are critically important for public health, there has been a major research effort in recent years to identify the responsible environmental, genetic, social and lifestyle factors (Hruby et al., 2016). A growing body of evidence suggests that obesity and its associated co-morbidities may also have in utero origins; metabolic consequences associated with maternal health and lifestyle are hypothesised to contribute to the early life determinants of obesity and cardiometabolic disease in their offspring (Godfrey et al., 2017). Research in human cohorts and in experimental animals studies has suggested that there are critical periods of developmental plasticity which make an individual susceptible to earl life exposures such as obesity leading to lifelong effects on the physiology of the offspring (Gaillard, 2015; Godfrey et al., 2016; Menting et al., 2019). Given the evidence for the early origins of obesity, antenatal lifestyle interventions focused on manipulating diet and/or physical activity, are increasingly considered to be a potential strategy for prevention of childhood obesity which is supported by the latest recommendations from the WHO Ending Childhood Obesity (ECHO) report (World Health Organisation, 2016). There remain, however, very few studies which have addressed the hypothesis of antenatal determinants of obesity through follow-up of children from antenatal intervention studies.

This thesis focuses on the UPBEAT trial, a lifestyle randomised controlled trial of diet and physical activity in pregnant women with obesity. My primary aim was to investigate the influence of maternal obesity on offspring measures of body composition and cardiovascular function in early childhood. Further analyses explored the longer-term impact of the intervention on maternal diet, physical activity and body composition. Finally, combining the intervention and control arms for the purposes of cohort analyses, the maternal antenatal and postnatal determinants of obesity in the children were explored. Fundamental to this work is the understanding of the epidemiology of obesity, with a focus on the associations between obesity in pregnancy and childhood outcomes.

Chapter 1 Introduction

1.1 Definition of overweight and obesity

1.1.1 Adult population

The World Health Organisation (WHO) define overweight and obesity as 'abnormal or excessive fat accumulation that may impair health' (World Health Organisation, 2014a). Despite being an indirect measure of body composition (as it does not distinguish between fat mass and fat-free mass) the body mass index (BMI) is used globally as a simple, non-invasive tool to classify adult overweight and obesity by calculating the ratio of body weight to height.

Although there is a strong correlation between fat mass (adiposity) and increasing BMI (Romero-Corral et al., 2008), for individuals with obesity BMI generally underestimates adiposity and there is a growing consensus that waist circumference or waist-to-hip ratio could be used to better estimate fat mass (Dalton et al., 2003). Despite these limitations, BMI is still a valuable screening tool for assessing body composition as it is an easy to perform method for assessing weight in adults. The BMI cut-offs for overweight and obesity are summarised in Table 1:1

1.1.2 Childhood population

The definition of childhood overweight and obesity is more complicated and there is currently no global consensus for the definition in a paediatric population (Dietz, 2017). During childhood and adolescence variations induced by growth, gender and puberty can influence the relationship between weight and height, therefore fixed thresholds for under 18 years of age are not appropriate. The WHO developed classifications derived from reference populations, irrespective of ethnicity and gender (de Onis, 2006). Infants and children up to 18 years of age can be compared to a reference population and the degree of variation from an expected value can then be calculated. These BMI thresholds are defined as Z-scores which are the number of standard deviations (SD) from the mean value. Overweight is defined as a z-score ≥2 SD and below <3 SD and obesity as a z-score ≥3 SD. Although these classifications are used across the world, limitations are apparent as a wide range of BMI can translate to a narrow range for a BMI z-score. Furthermore z-scores are on a linear scale, with the same intervals between each value therefore limiting its application to a population which has a skewed BMI distribution. Percentile curves may provide better estimates for defining obesity in children (Flegal and Cole, 2013) and these also have a

stronger correlation with measures of adiposity when compared to z-scores (Freedman et al., 2017). The International Obesity Task Force (IOTF) define obesity using gender specific percentiles, obesity in boys is >98.9th and in girls >98.6th (Cole and Lobstein, 2012). The WHO and the International Obesity Task Force classifications are summarised in Table 1:1.

Table 1:1 BMI classification and the corresponding centiles and z-scores for the IOTF and the WHO in children (aged 2-18 years)

		WHO classifications	IOTF classifications	
Adult classification	BMI cut-off points (kg/m^2)	z-scores	Boys	Girls
Underweight	<18.5	-2 SD	<15.5	<16.5
Healthy	18.5 - 24.9	-2 SD to 2 SD	15.5 to 90.4	16.5 to 89.2
Overweight	25.0-29.9	≥2 SD to < 3 SD	90.5 to 98.8	89.3 to 98.5
Obesity (class I)	30.0-34.9	≥ 3 SD	98.9 to 99.82	98.6 to 99.75
Obesity (class II)	35.0-39.9		≥99.83	≥99.76
Obesity (class III)	≥40.0	-	-	-

Abbreviations: BMI: Body mass index, IOTF: International Obesity Task Force, WHO: World Health Organisation

1.2 Epidemiology of obesity

1.2.1 Prevalence of obesity

1.2.1.1 Adulthood obesity

Globally, 650 million adults are estimated to have obesity, with prevalence slightly higher in women than in men (GBD Obesity Collaborators, 2017). In the UK nearly 30% of adults are

now obese (NHS, 2018), a substantial rise from 15% in the early 1990s (NHS, 2010). Obesity is also the most common medical condition in women of reproductive age (Catalano and Shankar, 2017), with over 20% of women in the UK entering pregnancy with obesity (RCOG, 2018), an increase from 7% reported in 1990 (Heslehurst et al., 2010). The proposed causes of obesity in adults, including antenatal populations are summarised in section 1.4.

1.2.1.2 Childhood obesity

Globally, the number of children under the age of five who are overweight or obese has risen dramatically. A joint report published by the United Nations Children's Fund, the World Health Organisation and the World Bank estimated that between 2000 to 2013 the number of overweight children increased from 32 to 42 million (World Health Organisation, 2014b) with global prevalence expected to reach 70 million by 2025 (World Health Organisation, 2016).

1.2.1.3 Childhood obesity as a precursor of adult obesity

There is evidence that the risk of obesity is already present at birth. Longitudinal modelling has also shown that higher birthweight (Geserick et al., 2018), overweight (Cunningham et al., 2014) or acceleration of BMI (Geserick et al., 2018) in early childhood can track through to the adolescent years. Once obesity is established in early life it often extends into adulthood; thus creating a life-long condition (Singh et al., 2008). Furthermore, as illustrated in Figure 1:*1*, given the current level of childhood obesity in the United States, predictive modelling estimates that nearly 60% of children today that reach adulthood will be classified as obese at the age of 35 years (Ward et al., 2017). The United Kingdom (UK) is no exception to increasing rates of childhood obesity; the recent figures from the National Child Measurement Program estimate that nearly a quarter of children under the age of five are overweight or obese, this statistic increases to a third by the time the child enters senior school (NHS, 2018). The UK can therefore anticipate a similar prevalence of adulthood obesity to the United States.

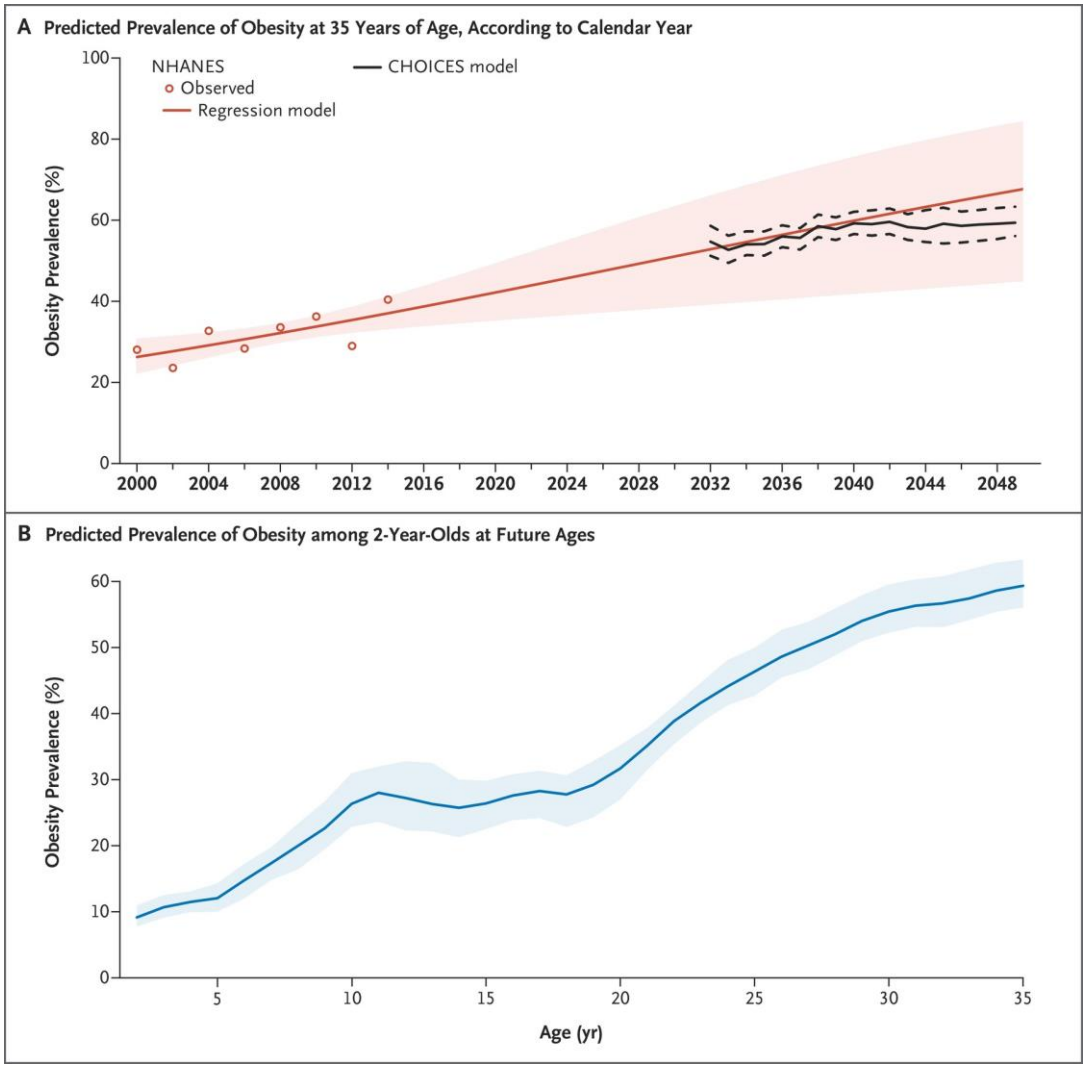


Figure 1:1: Predicted prevalence of obesity at the age of 35 years adapted from Ward et al. (2017).

Panel A shows the predicted prevalence of obesity at the age of 35 years among today's children from the CHOICES and NHANES cohorts. The 95% uncertainty intervals are indicated by a shaded area for the NHANES data and by dashed lines for the CHOICES model. Panel B shows the projected prevalence of obesity at future ages among 2-year-olds in 2016. The shaded areas indicate 95% uncertainty intervals.

1.2.2 Determinants of obesity

1.2.2.1 Adulthood obesity

The development of obesity is a complex health issue with no single determinant (Butland et al., 2007). Factors associated with the development of obesity in adults include social (Kuntz and Lampert, 2010), environmental (Hruby and Hu, 2015), lifestyle (Hankinson et al., 2010) and genetic (Lotta et al., 2019; Riveros-McKay et al., 2019; Rohde et al., 2019). In the UK, obesity prevalence is associated with higher deprivation indices (National Obesity Observatory, 2010), lower education attainment and ethnicity, specifically populations of

Black and Asian origin (El-Sayed et al., 2011). The global increase in obesity over the last 40 years suggests that although genetic variants may play a role (Wadden and Bray, 2018), lifestyle and environmental factors are the major two determinants (Hill et al., 2012) which may also interact with genetic traits to increase the risk of obesity (Huang and Hu, 2015) . Since the FTO gene was discovered, which has been shown to have a strong relationship with obesity, inflammation and appetite (Magno et al., 2018; Goltz et al., 2019), several further genetic variants related to obesity have been reported, however the size effect in relation to population obesity remains quite small (Frayling et al., 2007; Blauw et al., 2017). It has been suggested that genetics account for 1-2% of variation in BMI (Choquet and Meyre, 2011). Availability and intake of energy dense foods and excessive calorie consumption as well as a lifestyle which promotes low levels of activity all increase obesity prevalence (Mackenbach et al., 2014). Clustering of these social and environmental exposures has a significant impact on weight gain and the development of obesity. This has led to public health organisations highlighting the importance of identifying those groups affected by multiple exposures, so that strategies focused on obesity prevention can be personalised to focus on people most at risk of obesity related health outcomes.

1.2.2.2 Childhood obesity

Similarly to adult obesity, the aetiology of childhood obesity is multifactorial. The evidence highlights that increased adiposity results from environmental and psychosocial factors (Reinehr et al., 2017) as well as genetic (Aguilera et al., 2013) and family exposures (Boswell et al., 2019) which can either individually or through a combination increase a child's risk of developing obesity. There is also an evolving body of research, based on animal (Samuelsson et al., 2008; Drake and Reynolds, 2010), human epidemiological (Reynolds et al., 2013; Eriksson et al., 2014) and observational studies (Davey Smith et al., 2007; Gaillard et al., 2014a; Perng et al., 2014) which have demonstrated that childhood obesity is, at least in part, a consequence of exposures during fetal development, such as gestational diabetes (GDM) (Ruchat et al., 2013), excessive gestational weight gain (GWG) (Castillo et al., 2015) and maternal pre-pregnancy body mass index (Yu et al., 2013; Dalrymple et al., 2019a; Heslehurst et al., 2019), all of which implicate excessive fetal nutritional status. These exposures are discussed in detail in section 1.5.

These disturbances of the embryo/fetal antenatal environment, associated with maternal obesity, are thought to result in persistent biological modifications in the offspring, possibly

mediated through epigenetic pathways, which result in increased susceptibility of noncommunicable diseases such as a higher risk obesity, type 2 diabetes and an adverse cardiometabolic profile (Drake and Reynolds, 2010; Patel et al., 2015). Table 1:2 and Figure 1:*2* summarises the exposures which have been reported to be associated with childhood obesity.

Table 1:2**:** Associated causes of childhood obesity

	Risk factor
Intrauterine environment	Smoking (Oken et al., 2008) Maternal diet (Okubo et al., 2014) Gestational Diabetes Mellitus (Huang et al., 2007) Physical activity (Strong et al., 2005) Maternal obesity (Yu et al., 2013; Poston et al., 2016) Gestational weight gain (Castillo et al., 2015; Karachaliou et al., 2015) Birthweight (Martins and Carvalho, 2006; Rossi and Vasconcelos, 2010)
Diet	Infant milk diet (Arenz et al., 2004) Diet in early childhood (Dalrymple et al., 2019b) Consumption of sugary/fizzy drinks (Scharf and DeBoer, 2016)
Family environment	Socio-economic status (Lobstein and Millstone, 2007) Childcare (Neelon et al., 2015) Sleeping pattern (Miller et al., 2015) Physical activity (Tremblay et al., 2014)
Genetics	Siblings studies (Hawkins et al., 2019) Shared genetic traits (Frayling et al., 2007)

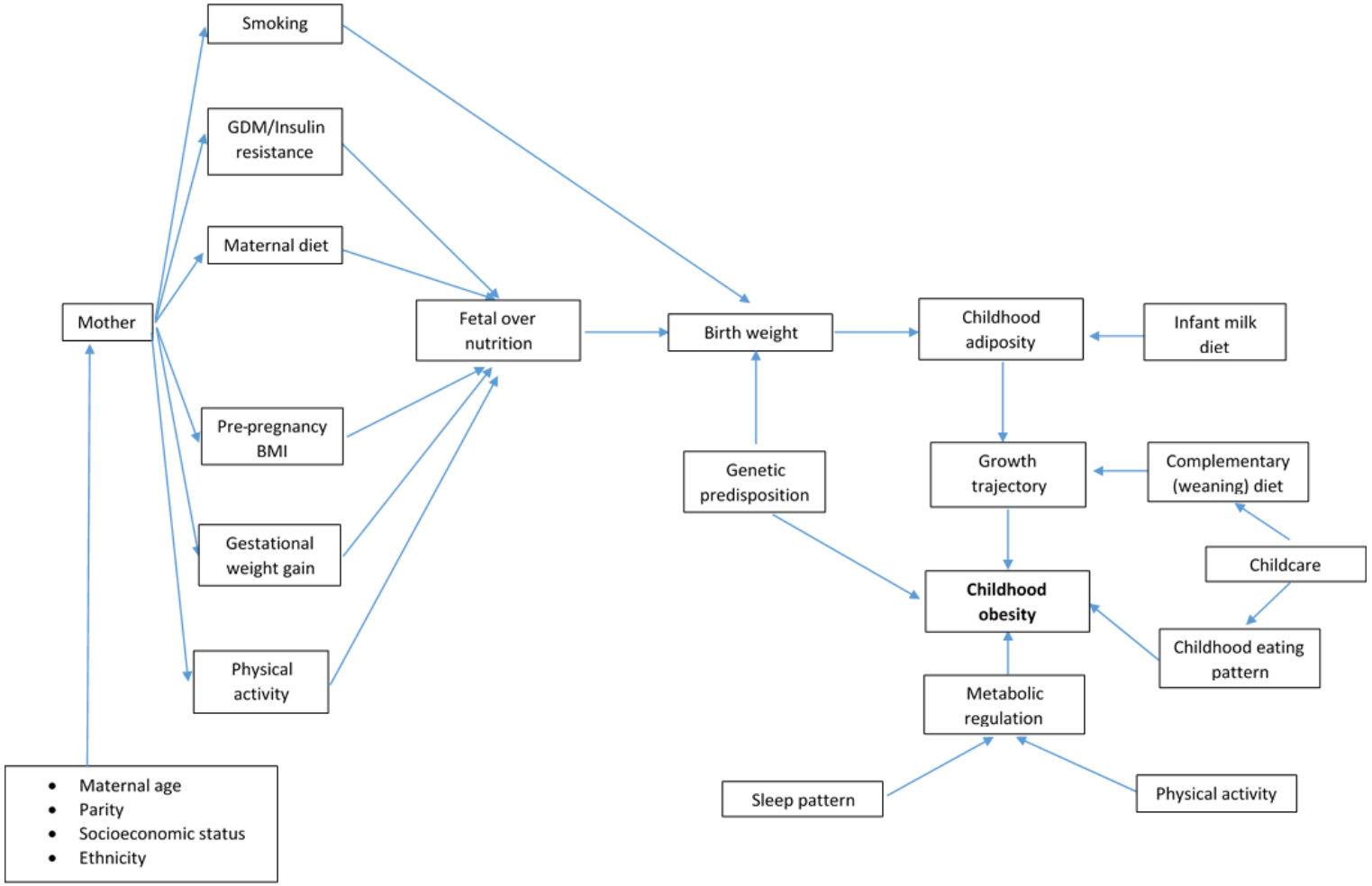


Figure 1:2: Overview of risk factors associated with childhood obesity

1.3 Health consequences associated with obesity

1.3.1 Adulthood consequences

Excess body fat which causes overweight and obesity is associated with several co-morbidities which can impact on quality of life and health outcomes, including hypertension, insulin resistance, atherosclerosis and physical health problems (Guh et al., 2009). Over time these conditions can manifest and conditions such as cardiovascular disease, type 2 diabetes and cancer can develop (Afshin et al., 2017). Obesity can also impact on quality of life and increase a patients' risk of low-self-esteem and depression (Nigatu et al., 2016). It is estimated that a 5% reduction in BMI in the European population would entail a 16.7% decrease in the prevalence of obesity related diseases such as cancer, stroke, and type 2 diabetes (Webber et al., 2014). The recent controversial campaign by Cancer Research UK has highlighted the strong relationship between obesity and cancer (Cancer Research UK, 2019).

1.3.1.1 Pregnancy and obesity

As this thesis focuses on children of obese pregnant women, the influence of obesity on the health of the mother should be appreciated, particularly since exposures to the maternal metabolic environment may be causal in the lifelong consequences of childhood obesity. Obesity in women of reproductive age can increase a woman's risk of infertility and can impact on in-vitro fertilisation success rates (Gillman and Poston, 2012). Maternal obesity is also associated with a number of pregnancy complications, including preeclampsia, GDM and caesarean delivery as well as an increased risk of miscarriage, stillbirth, congenital abnormalities and macrosomia (Poston et al., 2011). Depression and anxiety are also prevalent amongst obese women (Molyneaux et al., 2016; Poston et al., 2016). Less well appreciated is the evidence demonstrating that pregnancy *per se* is a major contributor to the development of obesity, through postpartum retention of weight gained during pregnancy (van der Pligt et al., 2013; Reynolds et al., 2020). This is particularly prevalent amongst women with GWG above that recommended by international guidelines; e.g. National Association for Medicine (NAM), formerly known as the institute of Medicine (IOM) (Linné et al., 2004; Institute of Medicine, 2009). This is further compounded by a positive relationship between pre-pregnancy overweight or obesity and gestational weight gain category (Sumithran et al., 2018).

Due to the known associations between pregnancy and weight retention during the reproductive years an emphasis on weight management before and between pregnancies has recently emerged. This is supported by a systematic review of intervention trials in the antenatal and postnatal period, which highlighted the importance of diet and physical activity in the postpartum period to support successful weight maintenance (Dalrymple et al., 2018a). However, there was insufficient evidence to conclude whether interventions which started in pregnancy were effective in overweight and obese women.

1.3.2 Childhood consequences

Childhood obesity is associated with both short and long-term health outcomes. In the short term compared to children with a healthy BMI, a child with obesity is more likely to experience psychiatric disorders, behavioural problems (Han et al., 2010) and low self-esteem (Reilly et al., 2003). These outcomes have been attributed to high body weight and negative self-image, with higher prevalence reported in girls compared to boys. A recent systematic review synthesised the evidence of associations between child and adolescent obesity and academic achievement. The authors reported that obesity is negatively associated with adolescent girls' maths achievement, with evidence suggesting that the association was mediated through body-weight related bullying (Martin et al., 2017). If these associations between early onset of obesity and academic attainment manifest into later life this could impact on employment prospects and socioeconomic status for the individual.

There is also substantial evidence which has consistently shown associations of obesity in childhood with long-term consequences later in life including mortality and cardiovascular morbidity (Owen et al., 2009). The adverse consequences of childhood obesity can also have immediate effects, including serious complications such as diabetes, fatty liver and asthma. Non-alcoholic fatty liver disease is now the most chronic liver disease in children and adolescents (Fitzpatrick and Dhawan, 2019) a consequence of the obesity epidemic. Bariatric surgery has been found to effective in reducing excess weight and co-morbidities in adolescents (Kumar and Kelly, 2017). These adverse consequences contributes to the increasing healthcare costs associated with earlier on set of obesity, as these children more frequently use healthcare services compared to children with a normal weight (Sonntag et al., 2016).

1.4 Aetiology of obesity

1.4.1 Pathophysiology

Adipose tissue performs a physiological role as an endocrine organ which stores energy in the form of fat (adipocytes) and provides a protective layer around internal organs (visceral fat) and is also found beneath the skin (subcutaneous fat). Adipose tissue metabolism is regulated by hormonal factors, notably insulin which leads to accretion of fatty acids (Coelho et al., 2013). Mobilisation of fat stores is responsive to energy needs. Adipose tissue itself secretes several bioactive products, including cytokines (adipocytokines) and hormones which can elicit systemic responses by influencing lipid and glucose metabolism as well mechanisms of central energy balance (Akoumianakis and Antoniades, 2017).

An imbalance between energy intake and energy expenditure leads to increased adiposity. Excess accumulation of adipose tissue is associated with metabolic dysregulation, altered glucose and lipid homeostasis and activation of inflammatory pathways which are considered to play and important role in the development of insulin resistance, cardiovascular disease and metabolic disorders (Ferranti and Mozaffarian, 2008; Oikonomou and Antoniades, 2019). Furthermore, the distribution of body fat has also been shown to influence health outcomes. Excess visceral fat which accumulates around the abdomen is associated with greater health risks, including incidence of cardiovascular disease and cancer (Britton et al., 2013) when compared to subcutaneous fat which usually accumulates around the hips (Snijder et al., 2006). A waist circumference > 102cm for men and >88cm for women is a risk factor for the development of type 2 diabetes, hypertension and cardiovascular disease (NICE, 2014), however these cut-offs have only been defined in a white European population and therefore may not be applicable to other ethnic groups.

1.4.2 The development of increased adiposity in childhood

An infant's growth and development are dependent on nutrition during the prenatal and postnatal period. Fetal overnutrition and rapid growth in infancy are associated with long-term overweight and obesity, through the accumulation and development of adipose tissue (Taal et al., 2013). An increase in adipose tissue mass can be achieved by two mechanisms: hyperplasia, an increase in adipocyte number, and hypertrophy, an increase in adipocyte size (Longo et al., 2019). In addition, the development of a mature adipocyte capable of fat storage requires differentiation of the stem cell precursor, the pre-adipocyte. The number

of pre-adipocytes which differentiate to form mature adipocytes has been proposed to be established in early childhood (Spalding et al., 2008), with a suggestion that the amount of lipids stored in each cell can change in response to energy balance. Some have suggested that early nutritional exposures can cause permanent changes in absolute adipocyte number (Symonds et al., 2012), therefore potentially predisposing a child to developing obesity. However, there is now considerable evidence that pre-adipocyte proliferation is dependent on endocrine mechanisms throughout life rather than being determined in early life (Sarantopoulos et al., 2018).

1.4.2.1 Adiposity rebound during childhood

Adipose tissue growth increases throughout the first 6-9 months of age at which point the infant reaches a peak in BMI z-score. Adiposity then generally declines for 3-6 years before the 'adiposity rebound' between the ages of 4-7 years (Cole, 2004). The age at which the adiposity rebound occurs has been shown frequently to be a risk factor for later obesity; children who experience adiposity rebound at an earlier age are reported to have a greater risk of increased adult BMI than children who experience it later in childhood. It has been proposed that the adiposity rebound may reflect differentiation of pre-adipocytes to mature adipocytes with the potential for later expansion and development of obesity (Rolland-Cachera et al., 1984; Whitaker et al., 1998).

1.4.3 The Developmental Origins of Health and Disease Hypothesis (DoHaD) and childhood obesity

The Developmental Origins of Health and Disease Hypothesis (DoHaD) suggests that certain environmental influences during critical periods of growth and development may have significant consequences on a child's short and long-term health. The field was substantially advanced by the work of Professor David Barker, indeed the hypothesis was originally attributed to him being known as the 'Barker Hypothesis' (Barker, 1995). Using retrospective data from UK longitudinal cohorts Professor Barker reported associations between low birth weight (as a surrogate for fetal undernutrition) and increased risk of hypertension and heart disease in adult life. Further to this, epidemiological insights for developmental 'programming' have been gained by analysing data from public health records during periods of famine. A relevant example is provided by the studies carried out in the Dutch Hunger Winter of 1944-1945. One of these reports showed that infants born before the famine compared to infants exposed to early and mid-gestation undernutrition demonstrated a

higher prevalence of disease in adult life, specifically obesity and diabetes (Roseboom et al., 2001). This is just one example of an extensive literature which has suggested that fetal undernutrition may lead to subtle changes in fetal phenotyping in early stages of fetal development (Fall, 2013). These studies have been extensively reviewed and are beyond the scope of this thesis (Langley-Evans, 2004) and have provided the basis of the current DoHaD concept which has now expanded to include a wide range of maternal and postnatal exposures, ranging from maternal obesity, pollution, socio-economic deprivation, smoking and maternal mental health (Hoffman et al., 2017). There is a consensus that environmental influences during critical phases of early *in utero* development can cause lifelong effects on the physiology of the offspring, especially structural and functional development of organs (Gluckman et al., 2005). As summarised in

Figure 1:3 it is suggested that the risk of developing chronic disease (including obesity) increases throughout the life course, but that becomes irreversible in later life as a result of declining 'plasticity' (green triangle). This is coupled with an accumulation of inadequate responses to new challenges (red triangle). This highlights the importance of intervening during the antenatal and early postnatal period to reduce the development of non-communicable diseases, including obesity.

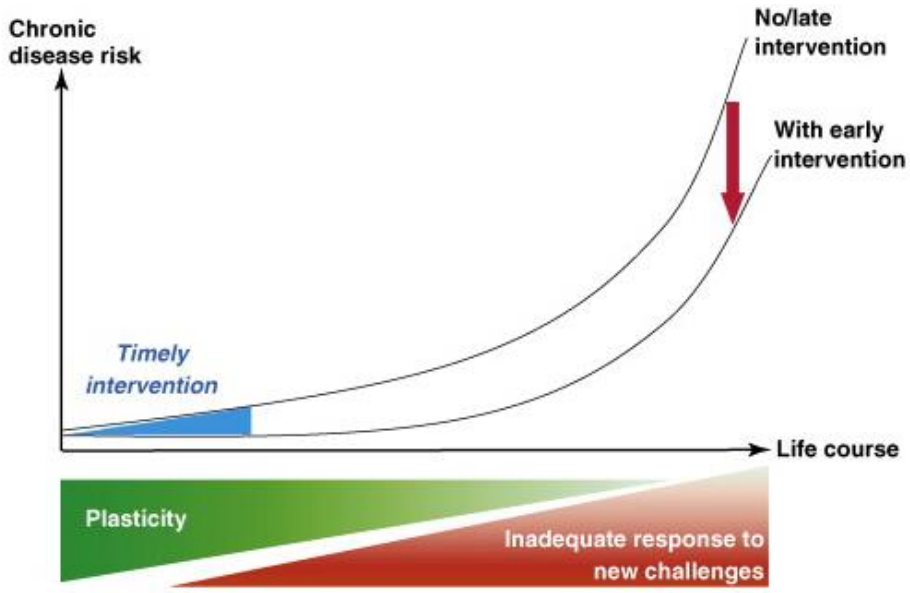


Figure 1:3 Importance of early intervention during the period of greatest developmental plasticity with regard to chronic disease risk in later life. Adapted from: (Godfrey et al., 2010)

In relation to the subject of this thesis, an extensive literature base suggests that childhood obesity may have origins in nutritional exposures during the first 1,000 days; from conception to 2 years of life (Woo Baidal et al., 2016). These include adverse nutritional exposures during *in utero* development (Lawlor et al., 2007) which have been independently associated with maternal obesity (Dalrymple et al., 2019a), tobacco exposure (Oken et al., 2008), excessive gestational weight gain (Gaillard et al., 2016a) and high birthweight (>4,000g) or macrosomia (Kristiansen et al., 2015). During the postnatal period rapid infant weight gain (Zheng et al., 2018), mode of feeding from birth (Rito et al., 2019) and food approach eating behaviours (Patel et al., 2018) have all been implicated in the development of obesity in early life. In order to develop appropriate interventions to optimise outcomes for both the mother and child, it is important to understand the proposed mechanisms which may contribute to the early origins to obesity during fetal and postnatal development.

Epidemiological observations of associations between early life nutrition and long-term disease risk have prompted detailed experimental investigation in animal models of the biological basis of programming. Studies using rodent or large animal models have clearly established the biological plausibility of nutritional programming have yielded important information on underlying mechanisms. Nutritional interventions in pregnancy, including food restriction (García et al., 2010), protein restriction (Bellinger et al., 2004), micronutrient restriction (Rao et al., 2012), excess fat feeding (Franco et al., 2012) and maternal obesity (Reynolds et al., 2017), have been implicated in a cluster of disorders in the offspring. The common association of such diverse nutritional disturbances with hypertension, glucose intolerance and adiposity suggest that a small number of simple common mechanisms are active in response to fetal nutrient imbalance. Numerous studies in experimental animals, including a series of reports from our department, have shown a relationship between maternal obesity and adverse outcomes in the offspring including increased adiposity, hypertension, increased sympathetic activity and metabolic dysfunction (Samuelsson et al., 2008, 2010; Drake and Reynolds, 2010; Menting et al., 2019). These studies have also suggested that overnutrition during pregnancy leads to permanent reorganisation of the hypothalamic neuronal network in the nuclei which control satiety and appetite regulation (Langley-Evans et al., 2005; Samuelsson et al., 2008; Kirk et al., 2009; Vickers and Sloboda, 2012). In models of maternal overnutrition the mediators of hypothalamic reorganisation are proposed to include fetal leptin, insulin and potentially corticosterone which arise from an increase in the plane of maternal nutrition. (Long et al., 2012; Tessier et al., 2013). Other suggested mechanisms include changes in the offspring epigenome and persistent changes

in fat mass (Ramamoorthy et al., 2018). These studies have been repeated across species (Long et al., 2012, 2015; Nathanielsz et al., 2015) and given that the animals are in a controlled environment, these many reports show unequivocal evidence for the maternal-child transmission of obesity and related co-morbidities in the animal kingdom.

Because of the described associations between early life exposures and offspring obesity and because plausible mechanisms have been identified, targeting the intrauterine environment and developmental pathway for prevention of childhood obesity is a rapidly evolving area of research, supported by the latest recommendations from the WHO Ending Childhood Obesity (ECHO) report (World Health Organisation, 2016).

1.5 Early life determinants of childhood obesity: Maternal exposures

As the scope of this thesis focuses on maternal obesity and weight gain in pregnancy as determinants of offspring adiposity, the background to these proposed associations is considered in more detail. Figure 1:*4* illustrates the overall associations between the maternal exposures discussed below and influence on offspring obesity.

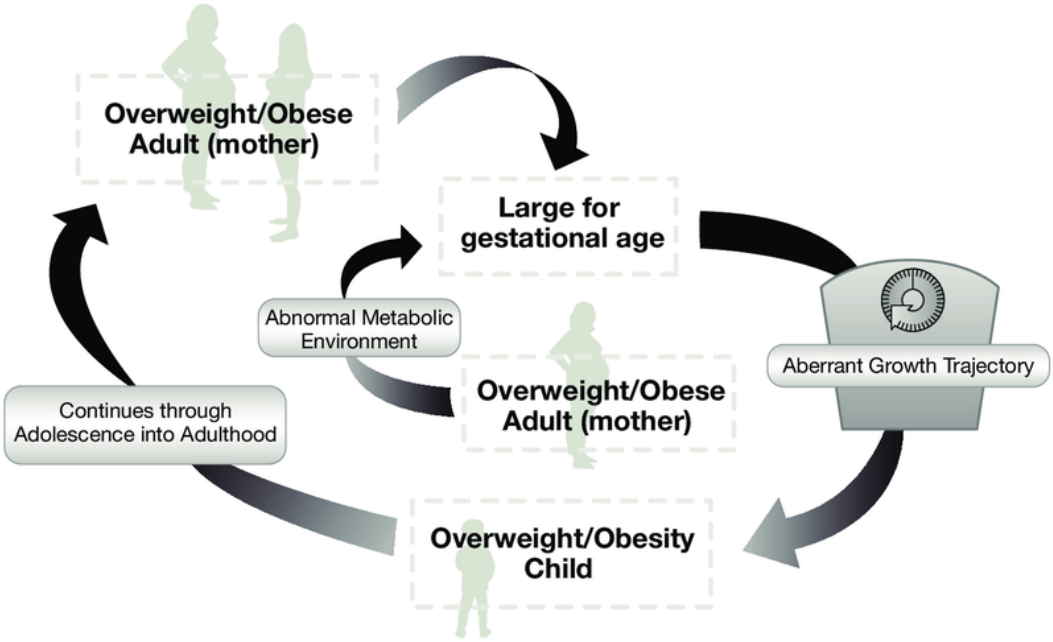


Figure 1:4 Intergenerational cycle of obesity. Adapted from (Adamo et al., 2012)

1.5.1 Maternal pre-pregnancy body mass index

Infants born to women with a higher pre-pregnancy BMI are more likely to have macrosomia (Lawlor et al., 2010), be classified as large for gestational age (LGA) and have an increase in body fat percentage (Catalano and Shankar, 2017). These associations have been shown to extend into infancy and early childhood. Observational studies have reported a relationship between maternal obesity and increased adiposity infancy (Lawlor et al., 2012; Jharap et al., 2017). A meta-analysis which investigated the relationship between pre-pregnancy BMI, infant birthweight and overweight or obesity in childhood and adolescence concluded that a pre-pregnancy BMI ≥30kg/m^2 increased the risk of LGA, macrosomia and obesity in childhood (odds ratio (OR) 2.08 95% CI 1.95-2.23; OR 3.23 95% CI 2.39-4.37; and OR 3.06 95% CI 2.68-3.49, respectively) (Yu et al., 2013). Additionally, mother-child cohorts from Generation R (Gaillard et al., 2013) and the Screening fOr Pregnancy Endpoint (SCOPE) study (Dalrymple et al., 2019a) have assessed the influence of maternal BMI on childhood obesity when the children were 4 and 6 years, respectively. Both studies reported an association between maternal and childhood obesity. A unique element of the SCOPE statistical analysis is that it analysed maternal BMI on a continuous scale (Figure 1:5) rather than categorical, therefore providing robust evidence, without loss of power, for an independent relationship between maternal BMI in early pregnancy and childhood adiposity at six years of age. More recently a meta-analysis of 79 studies (59 unique cohorts) identified a 264% increase in the odds of childhood obesity when a mother was obese before conception (Heslehurst et al., 2019). These epidemiological studies provide a strong rationale for an independent relationship between maternal and childhood obesity.

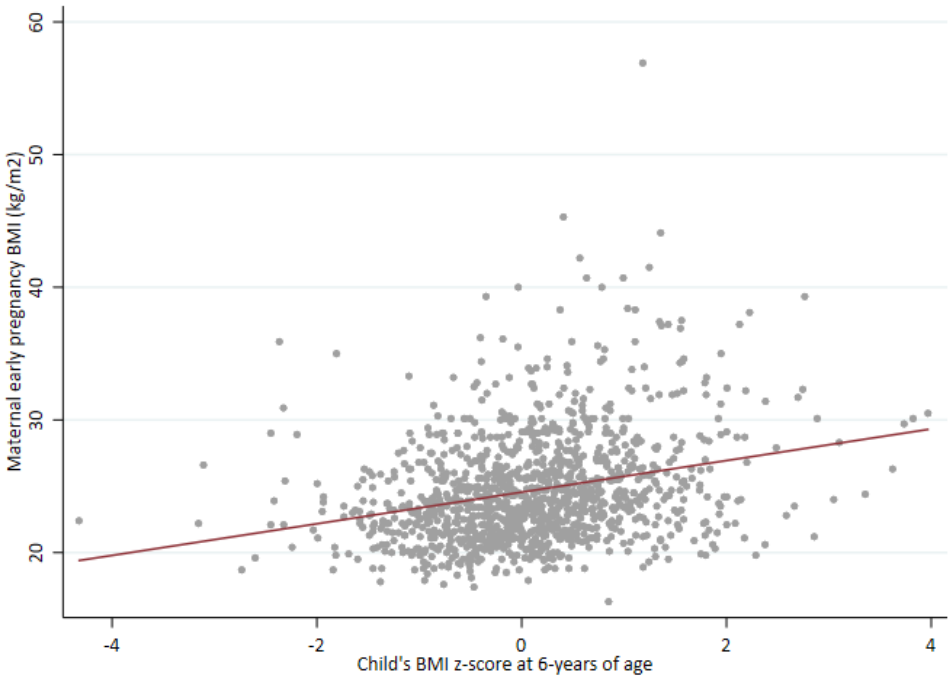


Figure 1:5. Associations between early pregnancy BMI and offspring BMI z-score at 6 years of age. (adapted from the SCOPE data, Dalrymple et al. 2019a)

As described in section 1.4.3 the description of experimental animal models and the metabolic disturbances of maternal obesity are considered to initiate persistent developmental changes in the fetus which then predispose the child to obesity and cardiovascular disease (Leddy et al., 2008). Further studies in human subjects have also suggested mechanisms which include maternal metabolic changes induced by glucose, lipids and fatty acids (Nelson et al., 2010), changes in placental function and inflammatory processes (Howell and Powell, 2017). Of interest, a recent investigation in the SCOPE cohort reported associations between higher placental growth factor (PlGF) and increased childhood obesity (Dalrymple et al., 2019a). We suggested that higher PlGF reflects increased placental angiogenesis and reduced vascular resistance. This could enhance nutrient transport across the placenta and predispose a child to increased adiposity (Helmo and Moed, 2007). The compelling findings from the human observational studies and experimental animal models suggest that obesity rates over subsequent generations are likely to accelerate, as the inter-generational cycle of obesity passes from mother to child (Cnattingius et al., 2012).

1.5.2 Gestational weight gain

The optimal pattern of weight gain throughout pregnancy has been and remains a matter of ongoing debate. In 1990, the NAM in the United States addressed this issue by defining recommended GWG depending on pre-pregnancy BMI (Table 1:*3*). In 2009, NAM revised its report, and published updated recommendations to optimise infant and maternal outcomes, with reference made to the associations between higher GWG, maternal postpartum weight retention and childhood obesity (Rasmussen et al., 2009). The relationship between excessive GWG and the risk of the offspring becoming overweight or developing obesity has recently been reviewed in a meta-analysis (Voerman et al., 2019), data summarised in Figure 1:6. Thirty-seven cohorts, including over 160,000 mother-child dyads found that excessive GWG was associated with an increased odds of overweight or obesity (OR 1.72 95%CI 1.56-1.91), with the strongest effects being reported at later ages in the offspring. Excessive GWG has also been shown to independently increase the risk of childhood obesity in large cohort studies, both in offspring of mothers with healthy pre-pregnancy BMI (Beyerlein et al., 2012) and mothers with overweight or obesity (Laitinen et al., 2012), highlighting that the associations between childhood weight development and excessive GWG is not limited to overweight and obese mothers. Gestational weight gain, however, has multiple components including maternal weight gain, fetus, placenta, maternal plasma volume expansion and amniotic fluid all of which vary with gestation. It is therefore difficult to attribute causality between any of these components of GWG and the association with offspring obesity. However, GWG could be seen as a surrogate for maternal lifestyle and excessive GWG has been associated with higher maternal pre-pregnancy BMI, sociodemographic characteristics, psychological factors and reduced physical activity (Samura et al., 2016). Therefore, GWG could be a mediator between these lifestyle characteristics and childhood obesity.

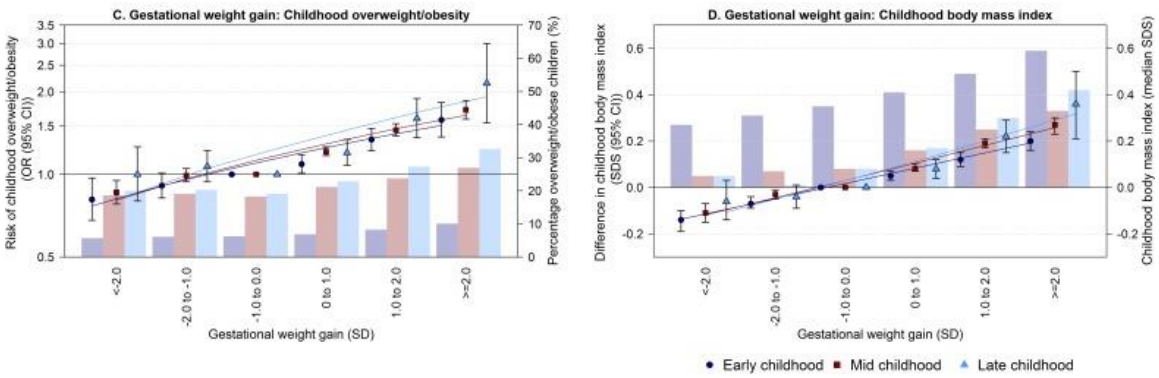


Figure 1:6: Associations of maternal gestational weight gain with the risk of overweight/ obesity and childhood BMI. (Adapted from Voerman et al. 2019)

Some observational studies have suggested the excessive GWG may have different effects of the fetus depending on when the weight gain occurs (Karachaliou et al., 2015). Data reported by the Generation R cohort has found that higher weight gain in early pregnancy is associated with adverse cardiometabolic outcomes in the children at six years of age (Gaillard et al., 2015). The authors suggested that the association between early weight gain and offspring cardiometabolic profile may reflect maternal fat mass which could lead to a higher transfer of nutrients across the placenta, including glucose, free fatty acids and amino acids, which could result in phenotype alterations in the developing fetus. Further to this, a recent report from the Hyperglyceamia and Adverse Pregnancy Outcome (HAPO) Study found that in 905 mother-child dyads, excessive and inadequate GWG were independently associated with childhood adiposity, hypertension and insulin resistance at 7 years of age (Tam et al., 2018). The authors hypotheses that these associations may be the role of shared familial behaviours, such as diet, physical activity or socioeconomic status. However, after adjusted for these confounding variables the results remain statistically significant. Therefore, these studies as suggestive of a direct relationship between maternal GWG and childhood outcomes.

A known limitation of these studies is the methodology used to estimate gestational weight and the various components which contribute to weight gain will differ between women (Gillman, 2012). This is reflected in the wide range of weight gain recommendations for each BMI category (Table 1:*3*). The National Academy of Medicine also highlight in their 2009 report that the data, for which the recommendations are based on, is not representative of various socioeconomic groups and ethnic minorities, which limits the translation of the

guidelines across other population groups. Currently in the UK there are no formal guidelines on GWG, and women are not routinely weighed at antenatal appointments.

Table 1:3: NAM guidelines for gestational weight gain by BMI category

Pre-pregnancy BMI	BMI cut-offs kg/m^2	Total weight gain (kg)	Rate of weight gain from 2nd to 3rd trimester (kg)
Underweight	< 18.5	12.5 - 18.0	0.51 (0.44 - 0.58)
Healthy weight	18.5 - 24.9	11.5 - 16.0	0.42 (0.35 - 0.50)
Overweight	25.0 - 29.9	7.0 - 11.5	0.28 (0.23 - 0.33)
Obese	>30.0	5.0 - 9.0	0.22 (0.17 - 0.27)

Abbreviations: BMI: Body mass index, NAM: National Academy of Medicine

1.5.3 Gestational Diabetes Mellitus

Separately from pre-pregnancy BMI and GWG, the development of the pregnancy complication gestational diabetes mellitus has been associated with increased offspring obesity (Zhao et al., 2016) and diabetes (Poston, 2010). GDM is defined as glucose intolerance (hyperglycaemia) which presents itself during pregnancy. Dependant on diagnostic criteria and population risk, the global prevalence of GDM is reported to be between 1-14% (Bain et al., 2015). The obesity epidemic is considered a major determinant for the development of GDM, and current prevalence in pregnant women with obesity in the UK has been reported as approximately 26% (IADPSG criteria) as reported in UPBEAT (Poston et al., 2013). Ethnicity, maternal age and previous history of GDM are also known risk factors (Lee et al., 2018).

Normal pregnancy is associated with metabolic changes, including insulin resistance (Catalano et al., 1998). The development of insulin resistance in pregnancy leads to mild maternal hyperglycaemia which facilitates glucose transfer to the developing fetus (Catalano et al., 1998). The global increase in maternal obesity is of particular concern, as the development of obesity is associated with inflammation, hyperinsulinemia, insulin resistance and mitochondrial dysfunction (Ye, 2013). Therefore, women with obesity of reproductive age are more likely to be insulin resistant before conception and are at risk of developing GDM in pregnancy compared to women of a healthy BMI.

A strong relationship has been reported between GDM in pregnancy and increased birthweight (Metzger et al., 2008; Yang et al., 2018). The proposed mechanism behind this association suggests that maternal hyperglycaemia leads to hyperglycaemia in the fetus as

glucose is transferred across the placenta. This results in an increase in insulin secretion by the fetal pancreatic islet cells and the increase in insulin stimulates fetal growth (Dabelea and Crume, 2011; Plows et al., 2018). There is some preliminary evidence that as in the animal models (Garcia-Vargas et al., 2012), maternal GDM is associated with hypothalamic dysfunction, as evidenced by increased hypothalamic blood flow, in response to a glucose challenge (Page et al., 2019) which may predispose the fetus to future risk of obesity.

1.6 Early life determinants of childhood obesity: Postnatal dietary exposures

1.6.1 Mode of infant feeding

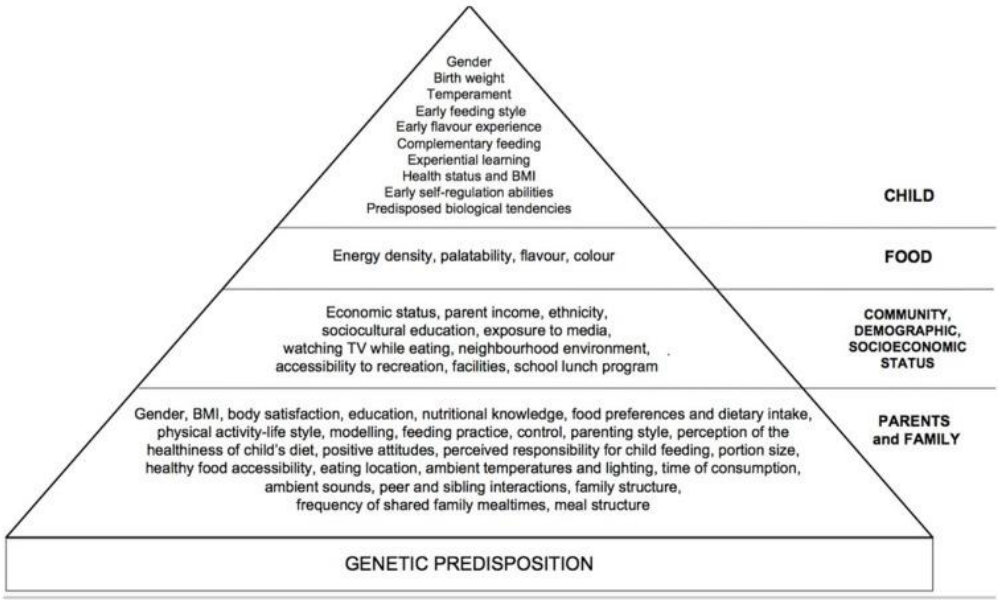
The WHO recommend that all infants are exclusively breast fed until 6-months of age. However, less than 1% of mothers in the UK adhere to this guideline (World Health Organisation, 2001; McAndrew et al., 2012). There are suggestions that early introduction of formula milk can increase the risk of obesity and adiposity in infancy and early childhood (Koletzko et al., 2009a; Victora et al., 2016). Some studies do not confirm these associations and have reported inconsistent results for the protective mechanism of breastfeeding against obesity (Yan et al., 2014; Woo Baidal et al., 2016). This may be the result of confounding factors, as duration and exclusivity of breastfeeding vary across these reports. Furthermore, the evidence base for the benefit of breastfeeding in primarily from observational trials and this may result in confounding of data, demographic characteristics of mothers who breast feed vs those who formula feed often differ, such as, education, IQ, age, maternal BMI, social support and socioeconomic status (Beyerlein and von Kries, 2011). Therefore, due to the heterogeneity in study methodology conclusive evidence is difficult to obtain. The largest RCT of promotion of breastfeeding (PROBIT trial) assessed breastfeeding duration and exclusivity with childhood outcomes in 31 maternity hospitals in Belarus (Kramer et al., 2001). Over 17,000 mother-infant dyads, who initiated breastfeeding, were randomised to the trial. The intervention arm used a behaviour approach to promote breastfeeding, specifically initiation and maintenance of breastfeeding, and the control arm was standard practice. This multi-centre RCT showed that the intervention was associated with an increase in duration and exclusivity of breastfeeding at 3 and 6-month postpartum (43.3% vs 6.4% an 7.9% vs 0.6%, respectively), which was associated with a low risk of gastrointestinal tract infections and atopic eczema in infants at 12 months of age (Kramer et al., 2001). However, longer-term follow-ups of the mothers and their children from PROBIT has shown that the intervention was not associated with lower measures of obesity and adiposity at 11 years of age (Martin et al., 2013). For ethnical reasons it would not be possible

to randomise infants to receive formula milk instead of breastmilk from birth. As all women recruited to PROBIT initiated breastfeeding the proportion of women who stopped breastfeeding during the first 12-month decreased in both arms of the trial. Therefore, the overall null findings of the effect of breastfeeding on childhood adiposity may be diluted as there was no control arm for formula fed infants. Furthermore, the prevalence of overweight and obesity is substantially lower in Belarus compared to the UK (~10% vs ~25%) (Patel et al., 2011; NHS, 2015), therefore the demographics of the PROBIT cohort differ to other European countries.

Formula milk and breast milk differ nutritionally in a number of ways. Breast milk contains bioactive agents and hormonal factors such as insulin and leptin that support the function of the gastrointestinal tract, immune system, brain development and have been proposed to regulate early growth patterns, including adipocyte development (Mazzocchi et al., 2019). The composition of breastmilk also varies over the first 6 months of an infant's life. Colostrum present in the first few days is higher in protein and immunoglobulins as well as growth factors and minerals; whereas transactional milk from day 7-14 is higher in fat and mature milk is present from 2 weeks onwards. Formula milk brand are generally based on cow's milk composition with higher protein and lower fat content compared to breast milk (Koletzko et al., 2009a). Growth patterns among formula fed and breastfed infants differ substantially (Patel et al., 2018) and early growth patterns have been linked to obesity (Rito et al., 2019). Indeed, breastfeeding has been shown to promote a growth trajectory considered to protect against later life obesity (Johnson et al., 2014). Some studies suggesting that breastfed infants are able to respond to appetite regulation ad satiety cues from a younger age compared to formula fed infants (Breij et al., 2017) which would be protective against obesity. It has been proposed that formula feeding associated higher weight gain is causally related to the higher protein content of formula milk as demonstrated in the European Childhood Obesity Project (CHOP) (Koletzko et al., 2009a, 2009b). This study has shown that a higher protein content of infant formula is associated with higher weight in the first 2 years of life.

1.6.2 Dietary habits

Nutrition in early life is increasingly considered to be an important factor in the development of obesity which can be influenced by genetics, social and environmental factors. These are summarised in Figure 1:*7*.



BMI: Body Mass Index

Figure 1:7: Environmental factors that influence child eating behaviour. Adapted from (De Cosmi et al., 2017)

As food habits which are established in early life track in early childhood, dietary habits in infancy have been shown to be prospectively associated with the development of childhood weight gain (van Jaarsveld et al., 2014). There have also been numerous studies which have reported independent relationships between dietary intake and eating behaviours and the development of adiposity and obesity in early childhood. The studies on eating behaviours, which have unanimously utilised the Childhood Eating Behaviour Questionnaire (CEBQ) to assess eating behaviours in early life, suggest that there are significant relationships between weight status in childhood and positive scores for food responsiveness and enjoyment of food. With negative relationships reported for satiety responsiveness and slowness in eating (Spence et al., 2011; Eloranta et al., 2012; McCarthy et al., 2015). Dietary patterns have also been shown to be associated with the development of childhood obesity. A collaboration study of eight European cohorts (n=8341) has shown that children who maintain a processed dietary pattern or consume patterns high in processed and sweet foods present the most unfavourable changes in fat mass and abdominal fat across childhood (Fernández-Alvira et al., 2017). Furthermore, individual food groups have also been associated with the development of childhood obesity. High consumption of nuts, meat, and pizza (Wolters et al., 2018), energy dense foods (Lobstein et al., 2015) and a high protein intake (Hörnell et al., 2013) have been associated with higher adiposity and obesity. Furthermore, longitudinal

studies suggest that the development of these eating habits in early life are stable across the lifecourse (Northstone and Emmett, 2008; Schwartz et al., 2011). Therefore, a high responsiveness and enjoyment of food or an 'unhealthy' dietary pattern in early life could be indicative that the child is on a trajectory for later life obesity.

1.7 Maternal lifestyle interventions and childhood obesity

The World Health Organisation describe childhood obesity as "one of the most serious public health challenges of the 21st century" (World Health Organisation, 2011). A variety of exposures in early life have been identified as contributing factors to the childhood obesity epidemic. There is strong evidence from experimental animals and epidemiological studies which unequivocally report associations between maternal obesity, excessive gestational weight gain and/or GDM and adverse childhood health outcomes, including increased risk to obesity (Heslehurst et al., 2019; Menting et al., 2019) and cardiovascular dysfunction (Reynolds et al., 2013; Thornburg, 2015). Postnatal factors associated with the development of childhood obesity include, exposure to formula milk which has been shown to alter growth trajectories in early life. Once the child is weaned the development of eating styles and behaviours has been associated with excessive weight gain throughout childhood (Scaglioni et al., 2018).

The impact of obesity in pregnancy on maternal and neonatal outcomes have been extensively reviewed (Thangaratinam et al., 2012; Poston et al., 2016) and includes increased risk of gestational diabetes, preeclampsia, fetal macrosomia, caesarean section, congenital defects, and fetal and maternal death. To date, antenatal interventions in women with obesity have primarily focused on improving GWG, reducing the incidence of GDM, improving perinatal outcomes, changing diet and physical activity behaviours and reducing the incidence of LGA infants (Flynn et al., 2016a). The International Weight Management in Pregnancy (i-WIP) IPD Collaborative Network recently completed a meta-analysis of 36 trials from 16 countries which showed that diet and physical activity based interventions during pregnancy reduced GWG (−0.70 kg, 95%CI−0.92 to −0.48) and lowered the odds of caesarean section (OR 0.91, 95%CI 0.83 to 0.99) for women of heterogenous BMI, with no evidence of a differential effect for the BMI sub group analyses (i-WIP Collaborative Group, 2017). This global research effort focused on antenatal interventions to improve pregnancy outcomes has provided an unintended opportunity to investigate outcomes in the children and the

observed improvement in GWG need to be assessed alongside information on longer-term outcomes for the mother and child.

To truly address the relationship between maternal and offspring outcomes, well designed randomised controlled trials (RCTs) are required. RCTs are powered to detect differences in pre-defined outcomes. Other secondary outcomes may be explored, but with the stipulation that the study design may not be powered to detect a meaningful difference between the trial arms. RCTs are also the only trial design which can address causality. Randomisation of participants balances characteristics between the trial arms, therefore an RCT yields an unbiased estimate for the observed outcome. To date, the Lifestyle in Pregnancy (LIP) (Vinter et al., 2011) is the only antenatal RCT in obese pregnant women to complete a follow-up in early childhood. Although, the intervention reduced maternal GWG there was no effect on offspring body composition at 2.8-years of age. However, the trial sample size was inadequate (n=157) to provide sufficient power to detect a difference between the groups (Tanvig et al., 2014). It is therefore crucial to assess the effect of large antenatal lifestyle intervention on childhood cardiometabolic outcomes and to better understand the short- and long- term effects of maternal obesity on offspring obesity and cardiovascular health in large groups of children. Furthermore, outcomes should be assessed according to maternal subgroups, such as maternal BMI, ethnicity and socioeconomic status, as it is important to ascertain whether the women and their children in these sub-groups benefit from these antenatal interventions (NICE, 2010). The i-WIP collaboration aim to complete an individual participant data meta-analysis (IPDMA), which includes the UPBEAT data, to evaluate the effects of lifestyle interventions in overweight and obese pregnant women, on both maternal outcomes and childhood adiposity at three to five years of age in approximately 3544 participants. The proposed IPDMA provides a unique opportunity to evaluate the effect of antenatal interventions in children born to women with overweight or obesity and the final results will be a welcome addition to the field (Dodd et al., 2017).

UPBEAT was a multi-centre randomised controlled trial comparing the effect of a lifestyle intervention of diet and physical activity advice to standard antenatal care in a large group of pregnant women with obesity, from UK inner-city settings of ethnic diversity and high social deprivation. The intervention focused on reducing dietary glycaemic load and saturated fat intake whilst increasing physical activity and was delivered from 15^{+0}-18^{+6} weeks' gestation for 8 weeks. 1,555 women were randomly allocated to the intervention or

to standard antenatal care. The results of the study indicated that the intervention had no effect on the primary outcomes, incidence of gestational diabetes and large for gestational age infants, between the groups. However, there was a difference in secondary maternal outcomes including a reduction in GWG (-0.55kg; 95%CI -1.08 to -0.02, p=0.041), sum of skinfold thicknesses (-2.3mm; 95%Cl -4.3 to -0.3, p=0.022) and an increase in physical activity (metabolic equivalent of task) (295METs; 95%CI 105 to 485, p=0.0015). The intervention also contributed to a healthier metabolic profile across pregnancy (Mills et al., 2019). At 6-months postpartum we found the maternal dietary benefits of the intervention were sustained and that the intervention resulted in lower infant subscapular skinfold thicknesses (Patel et al., 2017a). However, it remains to be determined, whether these observed changes during pregnancy have an influence on cardiometabolic outcomes in early childhood and are therefore investigated in this thesis.

The data reported in my PhD thesis is from the three-year postpartum follow-up of the mothers and children from UPBEAT. Firstly, I sought to investigate, through a systematic review, whether antenatal lifestyle interventions in pregnant women aimed at modifying diet and/or physical activity has led to a reduction in measures of offspring obesity in early childhood. Using the data from UPBEAT in the setting of a randomised controlled trial, I determined whether the intervention led to improved cardiometabolic outcomes in early childhood I also explored whether the antenatal intervention lead to a sustained improvements in maternal lifestyle behaviours three years after delivery. Furthermore, using the trial population as cohort, analyses explored the antenatal and postnatal determinants of obesity in the children.

As childhood born to women with obesity are risk of developing obesity themselves, the findings from this thesis from a cohort of solely women with obesity, provides invaluable insight into the exposures underpinning the relationship between maternal and childhood obesity. The findings will also help to inform public health strategies which can be personalised to focus on children most at risk of developing obesity and cardiovascular dysfunction.

1.8 Research Question and project objectives

The primary aim of this thesis was to examine the effect of an antenatal intervention on measures of offspring adiposity and cardiovascular function. Secondary aims were to describe the risk factors associated with the development of obesity in pre-school children.

1.8.1 Specific aims and objectives of this thesis

For this thesis, data from the UPBEAT study; an RCT assessing the influence of a dietary and physical activity intervention in pregnant women with obesity was used to address the following aims and hypothesis:

Aim 1: A systematic review of randomised controlled trials to evaluate the impact of antenatal lifestyle interventions on offspring adiposity in infancy and early childhood.

Objectives:

To undertake a systematic review to evaluate the impact of antenatal diet and/or physical activity randomised controlled trials on measures of offspring body composition and adiposity.

The review also defined associations between offspring adiposity and:

- The characteristics of the dietary and/or physical activity intervention.
- The method of intervention delivery.
- The effect of the antenatal intervention on secondary maternal and neonatal outcomes.

Aim 2: To determine the effect of a lifestyle intervention in pregnancy women with obesity on childhood adiposity and cardiovascular outcomes at 3-years of age.

Objectives:

To determine whether the UPBEAT intervention led to improved adiposity and cardiovascular function in the children at 3-years of age.

- According to maternal primary trial allocation to determine the difference in measures of adiposity and cardiovascular function in the children.
- To examine whether the antenatal intervention had a sustained effects on maternal diet and physical activity.

Aim 3: To investigate the associations between dietary patterns, eating behaviours and body composition and adiposity in 3-year old children of mothers with obesity.

Objectives:

- To describe the dietary intake in children at 3-years of age.
- Investigate associations of childhood dietary patterns and eating behaviours with measures of body composition.
- Explore the role of socio-economic deprivation on childhood dietary intake.

Aim 4: To examine the associations between maternal and early-life nutritional exposures and adiposity and obesity outcomes in 3-year old children.

Objectives:

- To identify the independent associations between six modifiable exposures including, early pregnancy BMI, , GWG, mode of infant feeding, and dietary intake and eating behaviours (food responsiveness and slowness in eating) with fourteen measures of offspring adiposity and obesity at 3-years of age.
- To develop a risk factor score and assess the incremental effect of the modifiable exposures on the childhood health outcomes.

Chapter 2 Methods

2.1 UK Pregnancy Better Eating and Activity Trial

2.1.1 Study design

This thesis is based on data from the UK Pregnancy Better Eating and Activity Trial (UPBEAT), an intensive lifestyle intervention of diet and physical activity in 1,555 pregnant women with obesity. UPBEAT (ISRCTN89971375; Chief Investigator Professor Lucilla Poston) was a multicentre randomised controlled trial, recruiting women from eight UK centres within inner city NHS trusts. The NHS trusts included London (Guy's and St. Thomas' NHS Foundation Trust, King's College Hospital Foundation Trust and St. George's University Hospital), Bradford (Bradford Royal Infirmary), Glasgow (The Southern General and Princess Royal Maternity Hospitals), Manchester (St. Mary's Hospital), Newcastle (Newcastle Royal Infirmary) and Sunderland (Sunderland Royal Hospital). NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application system; reference 09/H0802/5). All aspect of the trial; including data collection, monitoring and analysis were overseen by members of the UPBEAT consortium, as well as an external Trial Steering Committee.

2.1.2 Participants

Between March 2009 and June 2014 eligible women were identified in antenatal clinics and from general practitioner and midwife referral letters (Figure 2:1). Women over 16 years of age with a BMI ≥ 30kg/m^2, singleton pregnancy and gestational age between 15^{+0} and 18^{+6} weeks were invited to participate in the study. Women were excluded if they were unwilling or unable to give informed consent, if they had pre-existing diabetes, hypertension, renal disease, systemic lupus erythematous, antiphospholipid syndrome, sickle cell disease, thalassemia, coeliac disease, currently prescribed metformin, thyroid disease or current psychosis. Eight thousand, eight hundred and twenty women were assessed for eligibility and 1,555 were recruited to the UPBEAT trial (Figure 2:2) (Poston et al., 2015). Verbal and written information was provided to eligible women and for those who declined to participate, permission was sought to collect socio-demographic and pregnancy outcome data. At the first appointment, written informed consent was obtained from all participating women (Briley et al., 2014).

2.1.3 Randomisation

Participants were randomly allocated to either standard antenatal care or the UPBEAT intervention using a computer-generated randomisation procedure via a password protected internet-based data management system (MedSciNet™). Randomisation was minimised to ensure that the characteristics, summarised in box 2.1, were balanced between participants in the intervention and standard antenatal care.

Box 2.1 UPBEAT Randomisation criteria

- **Ethnicity**: Black, White, Asian, other
- **Parity**: primiparous, multiparous
- **Age**: ≤24, 25–29, 30–34, ≥35 years
- **BMI**: 30.0–34.9, 35.0–39.9, ≥40 kg/m²
- **Centre**: London (n=3), Bradford (n=1), Glasgow (n=1), Manchester (n=1), Newcastle (n=1) and Sunderland (n=1).

Due to the study design and intervention, study staff and participants were not blinded to intervention allocation. Data collected throughout the UPBEAT study was also stored on the MedSciNet system.

2.1.4 UPBEAT intervention

UPBEAT was designed to test the effect of an intensive lifestyle intervention focused on providing physical activity and dietary advice, with the aim of reducing the incidence of maternal Gestational diabetes mellitus (GDM) among women with obesity, and delivery of large for gestational age infants. The intervention was delivered over eight consecutive weeks between 15^{+0}-18^{+6} and 27^{+0}-28^{+6} weeks' gestation during face-to-face sessions with trained research staff. The intervention focused on improving insulin sensitivity through reducing dietary glycaemic load (GL) and saturated fat (SFA) intake and increasing daily physical activity.

Dietary component

The intervention aimed to alter dietary intake, without restricting energy intake, by encouraging participants to exchange starchy foods with a high glycaemic index (GI) for those with a lower GI (e.g white pasta for wholegrain pasta or cornflakes for porridge) and to

reduce the intake of sugar-sweetened drinks by swapping fizzy drinks, such as full-sugar Coca-Cola for diet alternatives (e.g Diet Coke, or Coke Zero) or full-sugar squash for squash with no added sugar. To reduce SFA intake, dietary advice included the use of low-fat dairy products and replacing fatty meats with lean meat and fish. All dietary recommendations were tailored to the women's personal and cultural preferences and are summarised in Table 2:*1.*

Physical activity component

The intervention included advice to increase physical activity which focused on increasing daily step counts and being more active in daily life, details of which are in Table 2:*1.* The advice was tailored to the women's pre-existing activity and additional options were provided for women who already engaged in exercise. Walking at a moderate intensity was encouraged in accordance with the UK Royal College of Obstetricians and Gynaecologists and pedometers were used for self-monitoring of daily step count. In addition, the participants received a DVD of an exercise regimen appropriate for pregnancy.

Delivery of intervention

Participants in the intervention arm were encouraged to attend weekly sessions for 1-1.5 hours with a study health trainer (clinical support staff trained in assisting behavioural change). The health trainers assisted the participants to change their behaviour to achieve personal choices and goals. All health trainers in this trial receive study-specific training in all aspects of the intervention and ongoing support throughout the trial. Women were advised to attend at least 5 of the sessions in person and if they were unable to attend a session the material was covered by email of over the phone. The overall premise of the UPBEAT intervention was developed on the basis of control theory (Webb et al., 2010), This theory suggests that behaviour change and identification of differences between current behaviours and future goals are indicative of personal behavioural monitoring. The intervention also focused on health promotion using social cognitive theory (Bandura, 2004). It is understood that health behaviours are determined by a number of core factors including; knowledge of health risks, perceived self-efficacy and the expected outcome for different health habits. Therefore, in the intervention sessions the participants developed personalised goals and strategies which encompassed SMART goal settings (specific, measurable, achievable, relevant and time-specific). They also received a handbook with guidance on making the changes along with recipe ideas and healthy eating during pregnancy

and a logbook to record dietary goals and daily step count which were reviewed on a weekly basis.

Table 2:1 Suggested diet and physical activity changes for the UPBEAT intervention arm

Dietary component	UPBEAT changes	Instead of this…	Choose this…
Glycaemic Load	Soft drinks	Regular soft drinks	Water and sugar free drinks including herbal tea
	Sugar	Sugar	Choose fruit to sweeten foods or artificial sweeteners
	Bread	Any type of white or brown bread	Multigrain and granary breads
	Rice and potatoes	Rice, mashed potatoes, chips	Basmati rice, pasta or new potatoes
	Breakfast cereals	Sugary cereals	Healthy cereals (Weetabix or Shredded Wheat) or porridge
Saturated fatty acid	Snacks	Chocolate, sweets, biscuits, cakes	Fresh fruit, low fat yogurts, cereal bars
	Dairy products	Full fat dairy products	Lower fat dairy products
	Meat and meat products	Fatty meat and meat products including meat pies, burgers and sausages	Lean meat, chicken, fish, and beans and pulses
Physical activity component		Suggested activities	Recommendation
Physical activity goals	Everyday activities	Increase daily step count	30 minutes of moderate exercise every day
		Walking at a moderate intensity	Pedometer provided to help keep track of step count
	Group activities	Swimming or exercising in water	Women were given a list of local group classes
		UPBEAT DVD	Try to do 20 or 30 minutes for a gentle safe workout

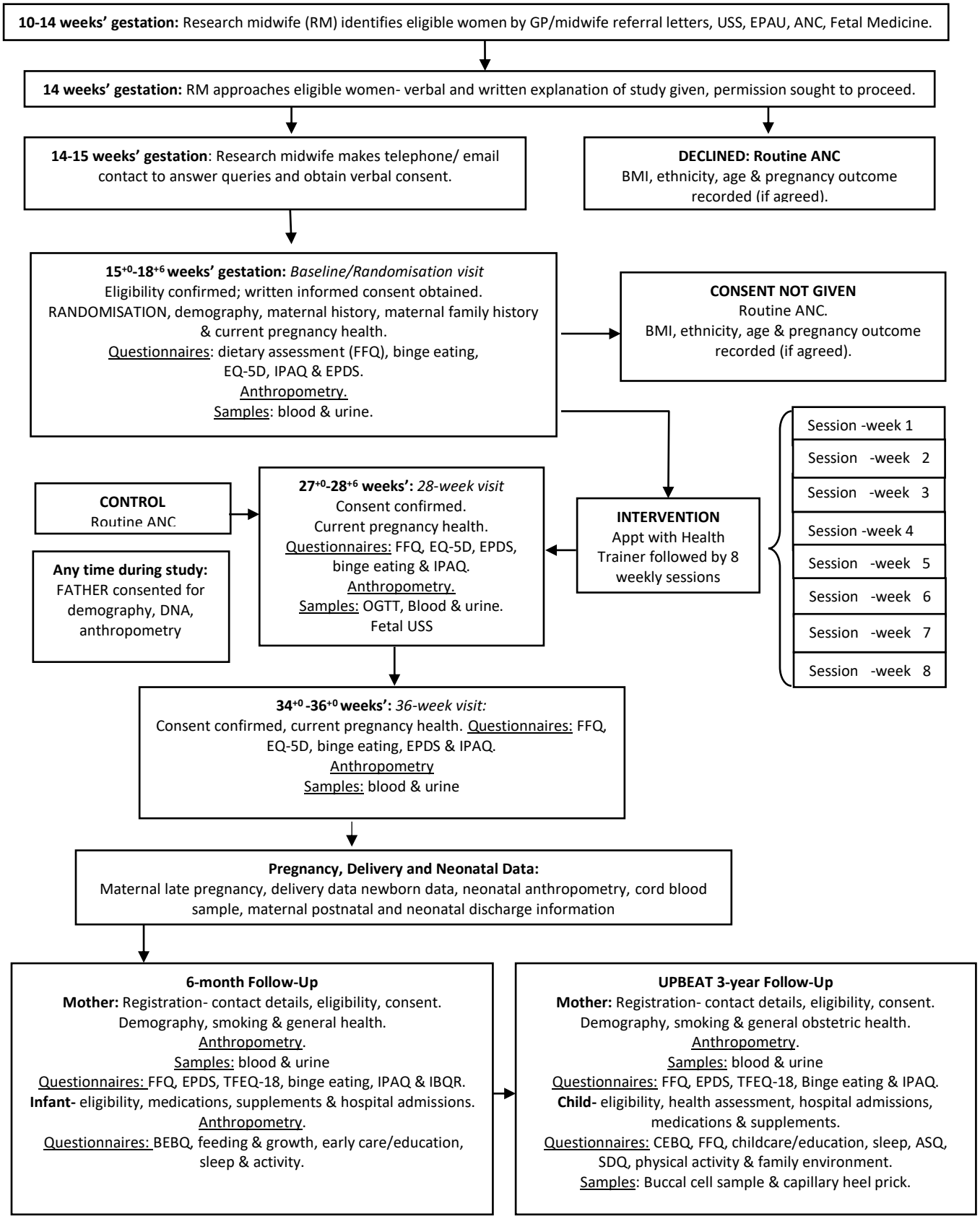


Figure 2:1 UK Better eating and Activity Trial Study protocol

Abbreviations: ANU: Antenatal care, ASQ: Ages and Stages, CEBQ: Childhood eating behaviour questionnaire, EPAU: Early Pregnancy unit, EPDS: Edinburgh postnatal depression scale, EQ-5D: Euroquol Health Questionnaire, FFQ: food frequency questionnaire, IBQR: infant behaviour questionnaire IPAQ: International physical activity questionnaire, OGTT: Oral glucose tolerance test, RM: Research midwife, SDQ: Strengths and Difficulties, TFEQ-18: Three-factor eating questionnaire, USS: ultrasound

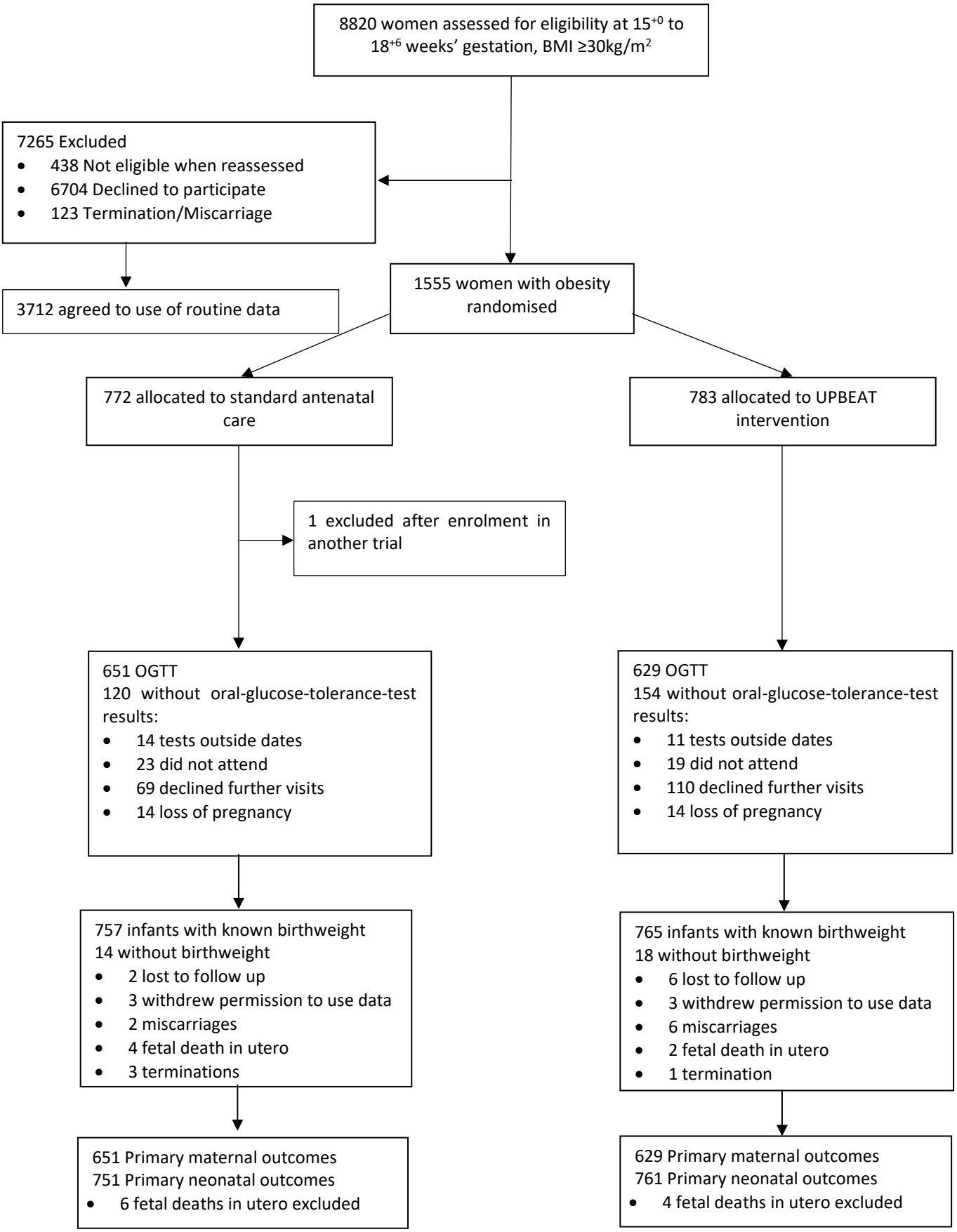


Figure 2:2: UK Pregnancy Better Eating and Activity Trial Consort diagram

2.1.5 Standard antenatal care

Participants randomised to both groups continued to attend routine antenatal care appointments at their local centre. The National Institute for Health and Care Excellence recommends that women with a BMI ≥30 kg/m^2 should be advised by a health care professional at first contact of the risks of obesity in pregnancy and be provided with healthy eating and physical activity advice (NICE, 2010). No additional information was provided to participants in the standard care group.

2.2 **UPBEAT data collection**

2.2.1 UPBEAT study assessment

All participants were asked to attend three study visits during pregnancy at 15^{+0}-18^{+6} weeks (baseline), 27^{+0}-28^{+6} weeks and 34^{+0}-36^{+6} weeks gestation and at 6-months postpartum. Infants were followed-up within 72 hours of birth and at 6-months postpartum. The study flow diagram is summarised in Figure 2:1. Trained research midwives or research assistants completed the data collection during the study visits and were provide with on-going face-to-face training and written standardised operating procedures for all data collection points throughout the duration of the trial.

2.2.2 Maternal dietary intake

A 50-item semi-quantitative food frequency questionnaire (FFQ) (Bingham et al., 2001) was completed and was used to assess micronutrient intake, total energy and dietary GL, GI, and total sugar intake. WISP 3.0 software (Tinuviel Software, Llanfechell, Anglesey, UK) was used by the UPBEAT study team to calculate the nutritional composition of diet across pregnancy and at 6-months postpartum. A Binge Eating Questionnaire (Gormally et al., 1982) and the Three Factor Eating Questionnaire (TFEQ) (de Lauzon et al., 2004) which assesses eating behaviour specifically cognitive restraint, hunger and disinhibition were completed.

Automated dietary analysis

An automated programme was developed in collaboration with the trial database team to transform food data from the FFQ into nutrient intakes for macronutrients, GL, GI and total energy intake, details of which are summarized in Figure 2:3.

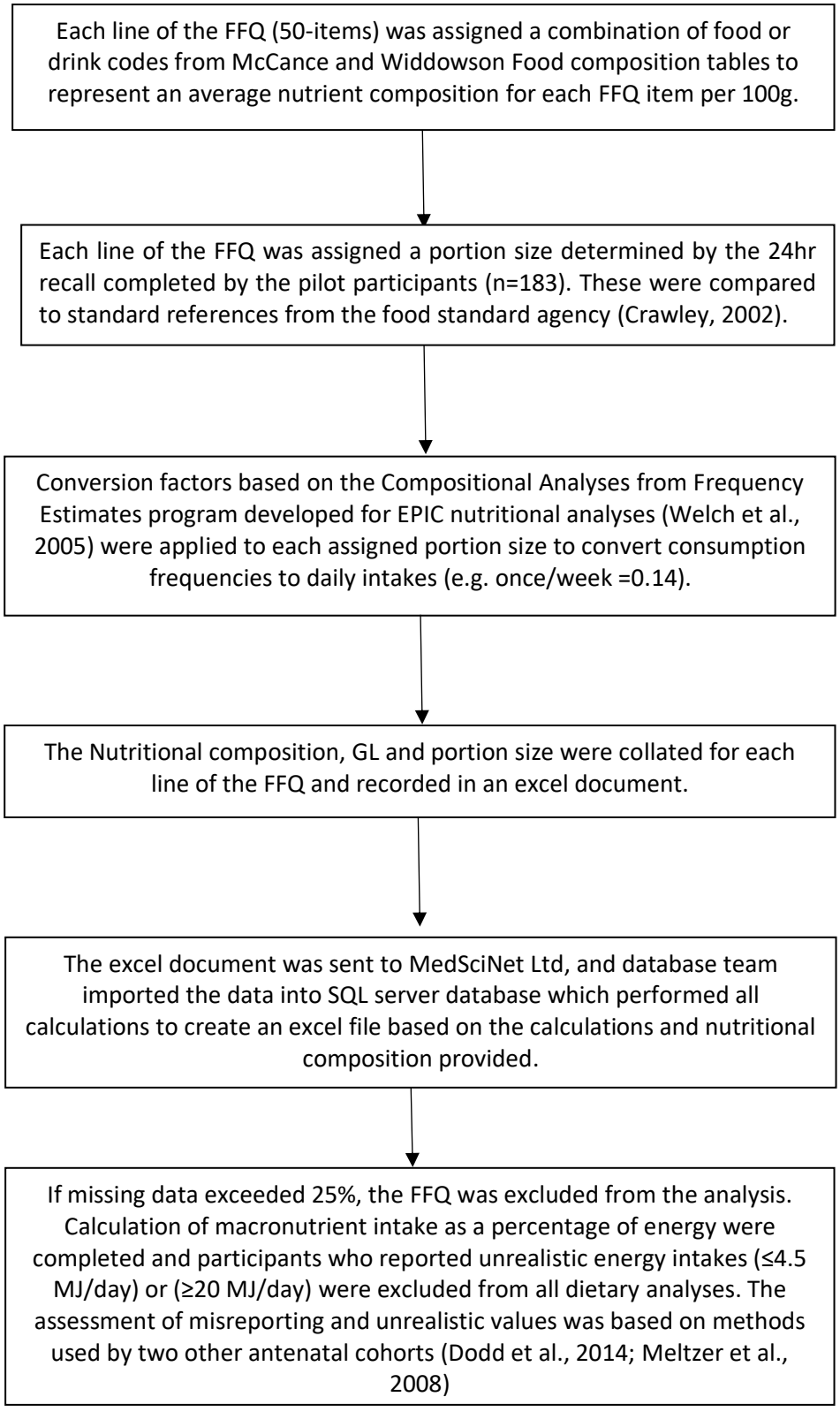


Figure 2:3: Methodology used to estimate daily macronutrient intake

2.2.3 Maternal anthropometric measurements

Anthropometry and body composition were assessed by measurement of skinfold thicknesses (subscapular, triceps, biceps and suprailiac; measured in triplicate using skinfold callipers) and waist, wrist, neck, mid arm, hip and thigh circumferences, data collection methodology is detailed in Table 2:2. The mother was weighed, using SECA scales to the nearest 0.1kg at each visit, and using height recorded at baseline, body mass index was calculated. Maternal gestational weight gain was recorded across pregnancy and calculated by subtracting pre-pregnancy weight from the measured gestational weight. Pre-pregnancy weight was estimated by subtracting 1.25kg from weight recorded at baseline (15^{+0} to 18^{+6} weeks' gestation). Weight gain guidelines from the National Academy of Medicine (previously known as the Institute of Medicine (IOM)) specify that 0.5-2.0kg is gained during the first trimester (Rasmussen et al., 2009), 1.25kg is the midpoint of this range and was chosen to subjectively estimate the weight gained in the first trimester. Total gestational weight gain was defined as the last recorded weight measured prior to delivery, minus the derived pre-pregnancy weight. All women were categorised within the gestational weight gain guidelines in accordance with the NAM criteria for women obesity, inadequate <5kg, adequate 5-9kg and excessive: >9kg (Rasmussen et al., 2009).

Table 2:2 Anthropometric measurements and associated methodology for data collection throughout the UPBEAT study.

Anthropometric measurement		Methodology
Circumferences	Waist	Circumference measured at the halfway point between the iliac crest and inferior margin of the lowest rib.
	Hip	Circumference from the maximal diameter of the buttocks.
	Thigh	Circumference measured from the observed largest part of the thigh.
	Mid arm	Circumference measured from the halfway point from the edge of the acromion to the tip of the elbow.
Skinfold thicknesses measured used Harpenden skinfold callipers	Triceps	Measured at the posterior aspect of the arm over the triceps muscle, at a midway point between the lateral projection of the acromion process of the scapula and the inferior margin of the olecranon process of the ulna.
	Biceps	Measured at the anterior aspect of the arm over the biceps muscle with the upper extremity relaxed to the side.
	Subscapular	Measured at inferior lateral border of the scapula with the calliper jaws placed infero-laterally, 45° to the horizontal plane.
	Suprailiac	Measured above the crest of the ilium.

2.2.4 Physical activity

The self-reported International Physical Activity Questionnaire (IPAQ) (Ekelund et al., 2006) was used to estimate frequency and intensity of physical activity. The questionnaire assesses walking, moderate-intensity and vigorous-intensity activities across the following domains: active leisure time, domestic and gardening activities, work-related physical activity and transport-related physical activity. All activities are assigned a metabolic equivalent of task (MET) score based on the ratio of energy expenditure during an activity to energy expenditure at rest (estimated at 8.0 for vigorous activity, 4.0 for moderate activity and 3.3 for walking) (Ainsworth et al., 2000). Using the following formula MET (minutes/week) was calculated, which indicate both the intensity and duration of an activity.

$$\text{Total MET} = [8.0\ x\ mins\ of\ vigorous\ activity] + [4.0\ x\ mins\ of\ moderate\ activity] + [3.3\ x\ mins\ of\ walking]$$

Total MET (minutes/week) were calculated from the IPAQ at baseline and at 27^{+0} to 28^{+6} weeks' gestation and the difference was used to indicate change in physical activity during the intervention period. To monitor any sustained improvement at 6-months postpartum, the IPAQ questionnaire was repeated at this timepoint. Women were categorised within the following three levels according to their self-reported activity levels:

Box 2.2: Categorical IPAQ scores

1. **Low**
   No activity reported, or some activity reported but not enough to meet categories 2 or 3.

2. **Moderate**
   5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week.

3. **High**
   7 or more days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/week

2.2.5 Additional variables

Cardiovascular function was assessed by blood pressure and resting pulse rate. Depression was assessed by the 10-question Edinburgh Postnatal Depression Scale (EPDS) (Cox et al.,

1987) was used to assess probable depression, defined as an EPDS score ≥ 13 (out of a possible 30). Blood and urine samples are also provided by the women.

Measures of Index of Multiple Deprivation

Socio-economic deprivation this was measured using the Lower Super Output Area (LSOA) which was collected from participants and corresponded to the census region of the participants home postcode. These were subsequently converted to the corresponding index of multiple deprivation quintiles (IMD) and subscales. As the IMD scores are not directly comparable across England and Scotland, a methodology proposed by Payne et al was used to combine the two regions; allowing generation of an adjusted index of multiple deprivation score using Scottish Index of Multiple Deprivation as a baseline (Payne and Abel, 2012). Through publicly available data; an adjusted IMD score was created using employment and income domains of the individual country together with coefficients and residual values generated by regression analyses of the overall IMD score and employment and income data. All participants were assigned an IMD score at baseline, this value was used in the analyses which included a measure of socio-economic deprivation.

2.2.6 Maternal metabolic profile

To assess how the metabolic profile changed over pregnancy metabolomics was utilized to quantity the low molecular weight molecules within blood samples of the participants. Metabolites are end products of enzymic processes and therefore a representation of the physiological process occurring with the women and may be indicative of the effect of the intervention. For the purposes of this analysis only, women from two centres (King's College Hospital, London, and Sunderland) were excluded as no blood samples were taken from participants in these centres (n = 360). Participants from the remaining centres had venous blood samples were taken on three occasions: baseline, 27^{+0} to 28^{+6} weeks' and 34^{+0} to 36^{+6} weeks' gestation. Samples taken prior to randomisation and in the third trimester were non-fasting; those taken at the end of the intervention (27^{+0} to 28^{+6} weeks') were taken after an overnight fast. All blood samples were initially kept on dry ice, processed within 2-hours and then stored at –80°C until metabolic profiling was performed.

2.2.7 Delivery data

At birth pregnancy outcome and neonatal data were collected, including mode of delivery, infant birthweight, length, mode of infant feeding and infant body composition assessed by skinfold thicknesses (triceps and subscapular, using infant skinfold callipers).

2.2.8 UPBEAT 6-month follow-up

At 6-months postpartum a planned follow-up was completed from May 2011 to June 2015, to determine whether the intervention led to sustained change in maternal dietary and physical activity behaviours. Diet and physical activity were assessed by the same questionnaires used during the UPBEAT intervention. Maternal demographic data, health since pregnancy and smoking status were obtained. Maternal anthropometric measures were repeated, by the trained research staff. To address safety and the influence of the intervention on the long-term health of the infant, details regarding the infant's health from birth were recorded and infant body composition and anthropometric measures were taken. The mothers were asked to complete an infant feeding and growth questionnaire, the Baby-Eating Behaviour Questionnaire (Llewellyn et al., 2011), a validated questionnaire assessing appetite responses and a revised infant behaviour questionnaire (Gartstein and Rothbart, 2003).

2.3 **UPBEAT summary**

2.3.1 Primary outcomes

For the original UPBEAT trial the intervention had no effect on the primary outcomes, incidence of GDM and LGA infants, results summarised in Table 2:3. GDM diagnosis was assessed in both arms of the trial with an oral glucose tolerance test (75g glucose load) at 27^{+0} to 28^{+6} weeks gestation. Participants diagnosed with GDM were referred for antenatal diabetic services. GDM diagnostic criteria were assessed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), which is summarised in Box 2.3

Box 2.3: Summary of IADPSG diagnostic criteria

- Fasting venous glucose of 5.1 mmol/L or higher
- 1 h venous glucose of 10.0 mmol/L or higher
- 2 h venous glucose of 8.5 mmol/L or higher, or a combination of these

For the neonate, LGA was defined as a birthweight ≥ 90th using a customised centile adjusted for maternal height, weight, ethnicity, parity, gestation at delivery, birthweight and sex.

2.3.2 Secondary outcomes

There was a difference in some of the secondary maternal outcomes including a significant improvement in maternal antenatal diet assessed by glycaemic load per day at 28 weeks' gestation, (mean difference – 21; (95% CI −26 to –16), *p*<0.0001) a reduction in gestational weight gain (-0.55kg; (95%CI -1.08 to -0.02), p=0.041), sum of skinfold thicknesses (-2.3mm; (95%Cl -4.3 to -0.3), p=0.022) and an increase in self-reported physical activity (295 METs; (95%CI 105 to 485), p=0.0015) (Poston et al., 2015).

2.3.3 Metabolome profile across pregnancy

The intervention also led to a healthier metabolic profile across pregnancy from baseline to 34^{+0} to 36^{+6} weeks gestation, for the control arm all very low-density lipoprotein (VLDL) particles increased by 1.5–3 SD and intermediate density lipoprotein and specific (large, medium and small) LDL particles increased by 1–2 SD, between the two timepoints. The UPBEAT intervention reduced the rate of increase in extremely large, very large, large and medium VLDL particles, particularly those containing triglycerides (Mills et al., 2019).

2.3.4 6-month postpartum follow-up

In total 698 (45.9%) infants (n=342 intervention and n=356 standard antenatal care), mean age of 5.9±0.69 months with their mothers attended the visit. For infants in the intervention arm there was a significant reduction in subscapular skinfold thickness z-score of -0.26 SD (95% CI −0.49 to −0.02; p=0.03). The mothers showed similar gestational improvements in dietary GL (−35.34; (95% CI −48.0 to −22.67); p<0.001) and saturated fat intake (−1.93%E; (95% CI −2.64 to −1.22); p<0.001) for the intervention arm at 6-months postpartum (Patel et al., 2017a). We have also reported, as part of cohort analysis, associations between measures of infant general appetite, assessed by the Baby Eating Behaviour Questionnaire, and infant body fat percentage, weight and growth after adjustment for confounders (Patel et al., 2018).

Table 2:3: UPBEAT primary and secondary outcomes by randomisation arm

		Intervention	Standard care	Effect of Intervention	p-value
Primary outcomes	N			Mean difference/ Risk ratio (95% CI)	
Gestational diabetes*	1280	160/629 (25%)	172/651 (26%)	0.96 (0.79 – 1.16)	0.68
Large for gestational age†	1512	71/761 (9%)	61/751 (8%)	1·15 (0.83 to 1.59)	0.40
Secondary outcomes					
Total Gestational weight gain‡	1093	7.19 (4.6)	7.76 (4.6)	−0.55 (−1.08 to −0.02)	0.041
Outcomes reported at 27^{+0} to 28^{+6} weeks' gestation					
Sum of skinfolds	1081	122 (26)	125 (27)	−3.2 (−5.6 to −0.8)	0.0081
Glycaemic load per day	946	112 (38)	133 (47)	− 21 (− 26 to – 16)	0.0001
Physical activity MET (min/week)	1147	1836 (792–4158)	1386 (639–3363)	295 (105 to 485)	0.0015

*Abbreviations: CI: confidence interval; MET: metabolic equivalent of task. Data are mean (standard deviation) or median (interquartile range). Gestational diabetes diagnosis by International Association of Diabetes in Pregnancy Study Group criteria at 27^{+0} to 28^{+6} weeks' gestation. † Customised birthweight centile adjusting for maternal height and weight, ethnic origin, parity and sex of the infant. ‡ Gestational weight gain calculated using estimated weight before pregnancy. § Calculated by addition of biceps, triceps, suprailiac, and subscapular skinfold thicknesses. Women with reported total energy ≤4·5 MJ/day or ≥20 MJ/day at 15^{+0}–18^{+6} weeks' gestation were excluded from analyses of diet *Physical activity estimates were calculated by bootstrapped (1000 replications) median regression, adjusting for pretrial values. MET is defined as the energy expenditure ratio of activity to rest; one MET is roughly equal to an individual's resting energy expenditure. MET, vigorous activity, moderate or vigorous activity, and walking were not prespecified endpoints.*

Table 2:4: Data collected throughout the UPBEAT and UPBEAT 3-year follow-up

Data collected	Questionnaire where appropriate	15^{+0}-18^{+6} weeks' gestation	27^{+0}-28^{+6} weeks' gestation	34^{+0}-36^{+6} weeks' gestation	Birth	6 months postpartum	3 years postpartum
Maternal							
Demography (Including socioeconomic status)		X				X	X
Diet	FFQ	X	X	X		X	X
	24-hour recall	X	X	X			
	Binge eating questionnaire						X
Physical activity	IPAQ	X	X	X		X	X
Clinical history	Hospital admissions	X	X	X	X	X	X
Clinical assessment		X	X	X	X	X	X
Anthropometry		X	X	X		X	X
Biochemical analyses		X	X				X
Metabolomics analysis		X	X	X		X	X
Neonate							
Clinical history	Hospital admissions				X		
Clinical assessment					X		
Anthropometry					X		
Metabolomics (cord)					X		
Infant							
Clinical history	Hospital admissions					X	
	Medicines & supplements					X	
Anthropometry						X	
Diet	Feeding and growth					X	
	BEBQ					X	
Lifestyle	Childcare					X	
	Sleep					X	

Child		
Clinical history	Hospital admissions	X
	Medicines & supplements	X
Anthropometry		X
Diet	FFQ	X
	CEBQ	X
Lifestyle	Childcare	X
	Sleep	X
Development	Ages and stages	X
	Strength and difficulties	X
	Physical Activity	X
Samples	Dried blood spot	X
	Buccal swab	X

Abbreviations: BEBQ: baby eating behaviour questionnaire; CEBQ: childhood eating behaviour questionnaire; FFQ: food frequency questionnaire; IPAQ: international physical activity questionnaire.

2.4 UPBEAT 3-year follow-up

2.4.1 UBPEAT 3-year follow-up

Between August 2014 and October 2017, all participants of the UPBEAT study were invited to attend a 3-year post-delivery visit with their child. Eligible women and their children were identified via the UPBEAT MedSciNet data management system and research records. Written informed consent was obtained from the mother for themselves and their child. Mothers who declined participation were asked for permission to keep contact details on record, for future follow-ups. Ethnical approval was obtained for the 3-year follow-up study, (UK Integrated Research Application System; reference 13/LO/1108).

2.4.2 UPBEAT 3-year follow-up data monitoring

Data was collected using a similar system developed for the main UPBEAT trial. An online study specific password protected database was created for all UPBEAT 3-year follow-up data (www.medscinet.net/upbeattempo; MedSciNet™). Throughout data collection for the UPBEAT 3-year follow-up monthly reports were generated by the clinical trials co-ordinator and included contact made with participants prior to the child's 4th birthday, recruitment timeline, data collection, and missing data. These reports were reviewed by the clinical trials team and the research midwives from the eight centres at a monthly teleconference. On a weekly basis data was checked by the clinical trials team and inconsistent or potential outliers were queried with the research midwife/research assistant through the MedSciNet database query log, where possible mothers were either contacted to clarify data entry or clinical notes were checked at the individual centre.

2.4.3 UPBEAT 3-year follow-up data dictionary

The main UPBEAT trial and UPBEAT 3-year follow-up collectively collected >7100 variables. To fully utilise the database and available data, two new data dictionaries were created for the maternal and child variables for the three-year visit. For the maternal data, to ease the import of data and data analysis, new names were derived from the original UPBEAT study variables by the addition of an "_3_" to identify the time point (for example maternal triceps skinfold thickness measured at baseline and the 3 year follow-up were detailed as follows; "*f22_sf_triceps_1*" changed to "*f22_3_sf_triceps_1*"). For the children's data new prefixes were used which had not already been assigned in previous datasets, (for example weight at three-years of age; *"f93t_3_wght".* f93 corresponds to the form, t corresponds to 'TEMPO'

(this was the internal acronym for the 3-year follow-up - The Effect of Maternal Obesity on Pediatric Obesity) and _3_ is the three-year visit, examples of the data dictionary are in Figure 2:4. For consistency across the main UPBEAT trial and UPBEAT 3-year follow-up datasets the same abbreviations were used to create variables names, e.g *weight = wght, height = hght.*

	A	B	C	D	E	F
1	Variable name a sexported	UPBEAT main trial variable	Variable explained	UPBEAT TEMPO variable		Variable options
202	BCO_Tricepsskinfold1	f22_sf_triceps1	Triceps skin fold (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_1	Triceps skin fold (1st measurement) of participant, at 3 years postpartum	Continuous
203	BCO_Tricepsskinfold1notmeasurable	f22_sf_triceps1_unkn	Triceps skin fold not measurable (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_1_unkn	Triceps skin fold not measurable (1st measurement) of participant, at 3 years postpartum	Yes No
204	BCO_Tricepsskinfold2	f22_sf_triceps2	Triceps skin fold (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_2	Triceps skin fold (2nd measurement) of participant, at 3 years postpartum	Continuous
205	BCO_Tricepsskinfold2notmeasurable	f22_sf_triceps2_unkn	Triceps skin fold not measurable (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_2_unkn	Triceps skin fold not measurable (2nd measurement) of participant, at 3 years postpartum	Yes No
206	BCO_Tricepsskinfold3	f22_sf_triceps3	Triceps skin fold (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_3	Triceps skin fold (3rd measurement) of participant, at 3 years postpartum	Continuous
207	BCO_Tricepsskinfold3notmeasurable	f22_sf_triceps3_unkn	Triceps skin fold not measurable (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_triceps_3_unkn	Triceps skin fold not measurable (3rd measurement) of participant, at 3 years postpartum	Yes No
208	BCO_Bicepsskinfold1	f22_sf_biceps1	Biceps skin fold (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_1	Biceps skin fold (1st measurement) of participant, at 3 years postpartum	Continuous
209	BCO_Bicepsskinfold1notmeasurable	f22_sf_biceps1_unkn	Biceps skin fold not measurable (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_1_unkn	Biceps skin fold not measurable (1st measurement) of participant, at 3 years postpartum	Yes No
210	BCO_Bicepsskinfold2	f22_sf_biceps2	Biceps skin fold (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_2	Biceps skin fold (2nd measurement) of participant, at 3 years postpartum	Continuous
211	BCO_Bicepsskinfold2notmeasurable	f22_sf_biceps2_unkn	Biceps skin fold not measurable (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_2_unkn	Biceps skin fold not measurable (2nd measurement) of participant, at 3 years postpartum	Yes No
212	BCO_Bicepsskinfold3	f22_sf_biceps3	Biceps skin fold (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_3	Biceps skin fold (3rd measurement) of participant, at 3 years postpartum	Continuous
213	BCO_Bicepsskinfold3notmeasurable	f22_sf_biceps3_unkn	Biceps skin fold not measurable (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_biceps_3_unkn	Biceps skin fold not measurable (3rd measurement) of participant, at 3 years postpartum	Yes No
214	BCO_Subscapularskinfold1	f22_sf_subscap1	Subscapular skin fold (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_1	Subscapular skin fold (1st measurement) of participant, at 3 years postpartum	Continuous
215	BCO_Subscapularskinfold1notmeasurable	f22_sf_subscap1_unkn	Subscapular skin fold not measurable (1st measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_1_unkn	Subscapular skin fold not measurable (1st measurement) of participant, at 3 years postpartum	Yes No
216	BCO_Subscapularskinfold2	f22_sf_subscap2	Subscapular skin fold (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_2	Subscapular skin fold (2nd measurement) of participant, at 3 years postpartum	Continuous
217	BCO_Subscapularskinfold2notmeasurable	f22_sf_subscap2_unkn	Subscapular skin fold not measurable (2nd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_2_unkn	Subscapular skin fold not measurable (2nd measurement) of participant, at 3 years postpartum	Yes No
218	BCO_Subscapularskinfold3	f22_sf_subscap3	Subscapular skin fold (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_3	Subscapular skin fold (3rd measurement) of participant, at 3 years postpartum	Continuous
219	BCO_Subscapularskinfold3notmeasurable	f22_sf_subscap3_unkn	Subscapular skin fold not measurable (3rd measurement) of participant, at 16+0 to 18+6 weeks	f22_3_sf_subscap_3_unkn	Subscapular skin fold not measurable (3rd measurement) of participant, at 3 years postpartum	Yes No

	A	B	C	D
1		Variable name as exported	Variable name	Variable explanation
269		Measured by parent	f93t_3_meas_parent	Antro measured by parent ?
270		MEAS - Weight	f93t_3_wght	Weight
271		MEAS - Height M1	f93t_3_hght_1	Height
272		MEAS - Height M2	f93t_3_hght_2	Height
273		MEAS - Height M3	f93t_3_hght_3	Height
274		MEAS - Height Mean	f93t_3_hght_m	Height _ mean
275		MEAS - Arm circumference M1	f93t_3_ac_1	Arm Circumference
276		MEAS - Arm circumference M2	f93t_3_ac_2	Arm Circumference
277		MEAS - Arm circumference M3	f93t_3_ac_3	Arm Circumference
278		MEAS - Arm circumference Mean	f93t_3_ac_m	Arm Circumference _ mean
279		MEAS - Waist M1	f93t_3_w_1	Waist
280		MEAS - Waist M2	f93t_3_w_2	Waist
281		MEAS - Waist M3	f93t_3_w_3	Waist
282		MEAS - Waist Mean	f93t_3_w_m	Waist _ mean
283		MEAS - Occipitofrontal circumference M1	f93t_3_oc_1	Occipitofrontal Circumference
284		MEAS - Occipitofrontal circumference M2	f93t_3_oc_2	Occipitofrontal Circumference
285		MEAS - Occipitofrontal circumference M3	f93t_3_oc_3	Occipitofrontal Circumference
286		MEAS - Occipitofrontal circumference Mean	f93t_3_oc_m	Occipitofrontal Circumference _ mean
287		MEAS - Arm 1 sBP	f93t_3_sbp_1	Arm

Figure 2:4: An extract of the UPBEAT data dictionary at 6-months and 3- years postpartum

2.4.4 Maternal data collection

The primary maternal outcome of interest for this thesis was to assess whether the dietary and physical activity improvements observed in the UPBEAT study were maintained three years after delivery.

Detailed maternal demographic, family environment, information on maternal health and pregnancies since the 6-month visit was obtained (Table 2:4). The maternal questionnaires completed as part of the main UPBEAT study were repeated, including the validated food frequency questionnaire, the Binge Eating questionnaire and the Three Factor Eating Questionnaire. Behavioural and psychological outcomes were assessed again by the EuroQuol Quality of Life Questionnaire, the International Physical Activity Questionnaire and the Edinburgh Postnatal Depression Scale (Cox et al., 1987). Anthropometry and body composition included measurement of skinfold thicknesses (subscapular, triceps, biceps, suprailiac, measured in triplicate by trained research staff using skinfold callipers), waist, wrist, neck, mid arm, hip and thigh circumference, the mother was weighed and her height recorded, and the BMI calculated. Cardiovascular function was assessed by blood pressure and resting pulse rate. Blood and urine samples were also provided by the mother. To ensure consistency of data collection the standardised operating procedure methodology developed for the main trial were repeated for the UPBEAT 3-year follow-up data collection.

Maternal dietary data collection

To ensure consistency across the main UPBEAT trial and the 3-year follow-up data collection time points, the methodology devised for the main UPBEAT trial to calculated maternal dietary intake (summarised in Figure 2:3) was used to calculate nutritional intake at the 3-year follow-up visit.

2.4.5 Offspring data collection

The primary offspring outcome for this thesis (defined *a priori)* was subscapular skinfold thickness, a measure of adiposity, in the children at 3-years of age. For the child, detailed anthropometric and body composition data was collection including weight, height, skinfold thicknesses (subscapular, triceps, biceps, suprailiac and abdominal), arm, waist, thigh and occipitofrontal circumferences and total body fat percentage by Bioelectric Impedance Assay (BIA), data collection methods are detailed in Table 2:5. Information regarding the child's stage of development (ASQ) (Squires and Bricker, 2009) and neuro development (SDQ) was

obtained (Goodman et al., 1998). Assessment of eating behaviours were completed using the Child Eating and Behaviour Questionnaire (CEBQ) (Wardle et al., 2001). The child's diet was assessed using an 85-item Food Frequency Questionnaire (FFQ). The list of food and drink items were compiled from the 80-item validated Southampton Women's Survey FFQ (Jarman et al., 2014) (further information section 2.4.11). Parent-reported information on the child's sleeping patterns was obtained by the validated Brief-Infant Sleep Questionnaire (BISQ) (Sadeh, 2004). Current childcare arrangements outside the home and nursery attendance were recorded. The mother was also asked about the child's health, any hospital admissions/outpatient attendances or medications since the 6-month visit. Blood pressure was recorded (systolic and diastolic) and resting pulse rate. All mothers were asked to consent for their child to provide a heel prick blood sample (Guthrie spot) and a Buccal cell sample. If preferred by the mother the FFQ, CEBQ, ASQ and SDQ were available for completion online or on paper prior to the appointment. If the mother and child were unable to attend in person, partial participation was offered, for this the mother was asked to complete the online questionnaires only.

2.4.6 Assessment of body composition

Methods for anthropometric data collected for the child is summarised in Table 2:5, sum of skinfold thicknesses, height, arm, waist, occipitofrontal and hip circumferences were measured in triplicate, weight and height were measured once.

Table 2:5: Childhood anthropometric measurements and the methodology for data collection in at the UPBEAT 3-year follow-up

Circumferences	Waist	Measured at the halfway point between the iliac crest and inferior margin of the lowest rib.
	Hip	Measured from the maximal diameter of the buttocks.
	Mid-arm	Measured from the halfway point from the edge of the acromion to the tip of the elbow.
	Occipitofrontal	Measured from the maximal diameter of the head.
Skinfold thicknesses – measured using Harpenden skinfold callipers	Triceps	Measured at the posterior aspect of the arm over the triceps muscle, at a midway point between the lateral projection of the acromion process of the scapula and the inferior margin of the olecranon process of the ulna.
	Biceps	Measured at the anterior aspect of the arm over the biceps muscle with the upper extremity relaxed to the side.
	Subscapular	Measured at inferior lateral border of the scapula with the calliper jaws placed infero-laterally, 45^{o} to the horizontal plane.
	Suprailiac	Measured above the crest of the ilium.
	Abdomen	Measured at a point 5cm horizontally to the left-hand side of the omphalion (midpoint of the navel).
Weight		Measured using SECA scales, with the child wearing pants only and weigh to the nearest 0.1kg.
Height		Measured using a Leicester height measurer, with the child's buttocks against the column with the head in the Frankfurt plane. Measure to the nearest 0.1cm.

2.4.7 Derived measures of childhood body composition

Child sum of skinfolds was calculated by addition of triceps, biceps, subscapular, suprailiac and abdomen skinfold thicknesses. WHO Child Growth Standards for height-for-age, weight-for-age, weight-for-height and BMI-for age, were generated from the WHO reference population and were adjusted for age and sex (de Onis, 2006). These reference populations are applicable irrespective of ethnicity and mode of early infant feeding. BMI-for-age was converted into BMI-centiles and the International Obesity Task Force gender-specific percentiles were used to define overweight and obesity in the children of UPBEAT (Cole and Lobstein, 2012) (Table 2:6).

Table 2:6: Centile equivalent cut-offs corresponding to the international BMI cut-offs

	BMI cut-off at age 18 (kg/m^2)	Centile Equivalent	
		Boys	Girls
Underweight	<18.5	<15.5	<16.5
Healthy	18.5-24.9	15.5-90.4	16.5-89.2
Overweight	25.0-29.9	90.5-98.8	89.3-98.5
Obese	30.0-34.9	98.9-99.82	98.6-99.75
Morbidly obese	≥35.0	≥99.83	≥99.76

Abbreviations: BMI: Body mass index

2.4.8 Body fat percentage

Estimated total body fat was calculated from the fat mass measured using the Bioelectrical Impedance Assay using the ImpediMed Imp SFB7. Before the measurement was completed the child was asked to remove jewellery, socks and to empty their bladder. They were asked to lie on their back in a fully supine position on the examination table, to extend their arms by their side, hands rested next to their body, palms down, with their legs slightly apart. During data collection their limbs should not cross and legs were completely separated. The electrodes were placed on the wrists and feet and estimated fat mass (kg), fat free mass (kg), total body water (litres), extra- and intra-cellular fluid (litres) were generated. Using the estimated fat mass, body fat percentage was calculated using the following equation:

$$\left(\frac{(Fat\ mass\ (kg)}{weight\ (kg)}\right) * 100 \ = \ body\ fat\ percentage$$

2.4.9 Cardiovascular outcomes

After the BIA was completed the child was asked to sit up, their bare right arm was supported and rested on the desktop (so the midpoint of the upper arm is at the level of the heart) back

and feet were supported, and their legs uncrossed. Blood pressure and resting pulse rate were measured using the WelchAllyn 53S00-E4 with the appropriately sized cuff for the child.

2.4.10 Physical activity

The parent reported questionnaire was based on the activity of the child when they were not attending nursery/pre-school, information on mid-week and weekend frequency of the specific activity and the duration of eight types of activity including organised classes, such as swimming or dance classes were collected. The questionnaire also asked two questions about time spent on non-active devices, such as electronic games, tablets, computers or phones and time spent watching TV. To estimate total weekly activity (n=8) and time spent on non-active devices (n=2) two new variables were created using the following formula:

$$\frac{(Mon - Fri\ freq * total\ minutes) + (Sat - Sun\ freq * total\ minutes)}{7} = total\ minutes/week$$

2.4.11 Dietary intake

The child's diet was assessed using at 85-item food-frequency questionnaire (FFQ), the list of food and beverage items were compiled from the validated Southampton Women's Survey (Jarman et al., 2014). Three questions were extended to include culturally appropriate options, e.g. "Rice-boiled & fried" to "Rice-boiled & fried jollof, rice and peas". Five additional food items, summarised in box 2.4, were included which were culturally appropriate for the non-white ethnic subgroups in the UPBEAT cohort (Black African/Caribbean).

Box 2.4. Additional food items added to the children's FFQ

- Hard dough, African bread
- Yam, cassava, fufu, kenkey, green banana, plantain
- African/Caribbean fish/shrimp soups
- African/Caribbean groundnut/peanut soups
- African/Caribbean vegetable soups e.g. okra, aubergine, tomato, spinach

The FFQ asked how often in the last three months the child had consumed each of the food and beverage items. The response options were never, less than once per month, 1-3 times per month, number of times per week (1-7) or more than once per day. If the food item was consumed more than once a day, the number of times was recorded. At the end of the FFQ additional information was collected relating to milk consumption and sugar added to food and/or drinks each day. This included information on the type and quantity of milk consumed and the number of teaspoons of sugar added to the child's food and drink. Frequencies of consumption and amounts of foods not listed in the FFQ were also recorded, if they were consumed once a week or more. Dose and frequency of dietary supplements taken in the preceding 3 months were recorded.

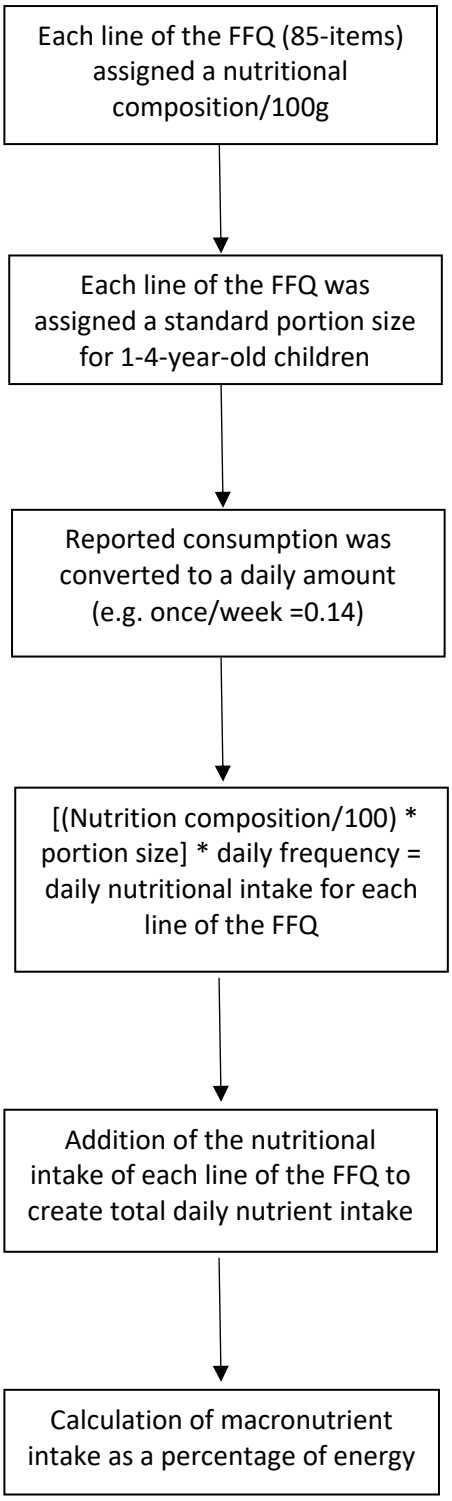


Figure 2:5 Methodology used to estimate daily macronutrient intake

2.4.12 Calculation of daily nutrient intake

The food and beverage items listed in Part 1 of the FFQ were assigned codes obtained from the 6th edition of McCance and Widdowson's Food Composition Tables (McCance and Widdowson, 2015), these were selected from the composition tables to represent an average nutrient composition for each food item as outlines in Table 2:7 below:

Table 2:7: An extract from the generated Food Composition Table and assigned codes for each line of the food frequency questionnaire

RICE, PASTA AND POTATOES (medium serving)	Food Name	Code
Boiled and Baked Potatoes	New potatoes, boiled in unsalted water	13-001
	New potatoes, in skins, boiled in unsalted water	13-420
	Old potatoes, baked, flesh and skin	13-010
	Old potatoes, baked, flesh only	13-011
	Old potatoes, boiled in unsalted water	13-421
Chips, waffles and potatoes shapes	Potato products, shaped, frozen, baked	13-425
	Chips, oven, frozen, baked	13-029
	Chips, retail, fried in vegetable oil	13-422
	Chips, French fries, retail	13-423
Roasted potatoes	Old potatoes, roast in blended oil	50-671
Pasta - boiled & tinned	Macaroni, boiled	11-448
	Pasta, plain, fresh, cooked	11-450
	Spaghetti, white, boiled	11-453
	Spaghetti, wholemeal, boiled	11-455
	Spaghetti, canned in tomato sauce	11-357

The nutritional composition/100g for each line on the FFQ were obtained for McCance and Widdowson and an average nutritional composition for each FFQ food item was generated. If multiple codes were assigned to one food or drink an average was generated.

2.4.13 Portion size

There are currently no UK guidelines for nutritional intake for 3-year-old children, to determine average portion size for each line of the FFQ data was obtained from a recent publication (More and Emmett, 2015), which summarises food portion sizes for 1-4 year olds based on data from the National Diet and Nutrition Survey and the Avon Longitudinal Study of Parents and Children (ALSPAC). Table 2:8 is an extract from the food portions table used to calculate daily nutrient intake.

Table 2:8: Extract of food portion sizes for 1-4-year olds

Breads and Crackers	
White bread	27g
Brown and wholemeal bread	27g
Crackers, cheese biscuits and breadsticks	15g
Hard dough, African Bread	34g
Potatoes, rice and pasta	
Boiled and Baked potatoes	52g
Chips, waffles and potatoes shapes	60g
Roasted potatoes	35g
Pasta - boiled & tinned	45g
Rice - boiled, fried, jollof, rice and peas	45g
Yam, cassava, fufu, kenkey, green banana, plantain	40g

2.4.14 Dietary analysis

To calculate nutrient intake from the FFQ, each assigned portion size was converted to a daily frequency outlined using the conversion table below (Table 2:9). The database team at MedSciNet imported the data into an SQL server database which performed all calculations and created an excel file of average nutritional intake using average portion sizes and estimated frequency. The methodology devised to estimate macronutrient intake is summarised in Figure 2:5.

Table 2:9: Conversion of consumption frequencies to daily amount

Never or less than once/month	0
1–3 per month	0.07
Once a week	0.14
2 per week	0.29
3 per week	0.43
4 per week	0.57
5 per week	0.71
6 per week	0.86
7 per week	1
more than once per day	(no of times per day)

Once the data was generated for daily nutrient intake for the children at 3-years of age macronutrient intake as a percentage of energy was calculated using the following formulae:

$$Carbohydrate\ (\%E)\text{: } [(CHO\ (g)\ x\ 3.75)/kcal]\ x\ 100$$
$$Fat\ (\%E)\text{: } [Fat\ (g)\ x\ 9)/kcal]\ x\ 100$$
$$Protein\ (\%E)\text{: } [(Protein\ (g)\ x\ 4)/kcal]\ x\ 100$$

2.4.15 Missing data and misreporting

To ensure there was no missing data in the food frequency questionnaires these were mandatory fields for the main care giver to fill in during the 3-year visit and the file would not save unless all data points were completed. Therefore, no questionnaires were excluded from analysis for missing data. The assessment for misreporting included unrealistic energy intakes; children who were reported to consume ≤500kcal/day or ≥2200kcal/day were excluded from the analysis.

2.4.16 Dietary pattern analysis

Dietary patterns of the children were derived using factor analysis. The food and drink items listed on the FFQ were categorised into 39 groups based on similar nutritional composition. Three additional items recorded as additional foods were also included: porridge/shredded wheat, fast food (McDonalds, Burger King and KFC) and cereal bars (Table 2:10).

Table 2:10: List of the 39 food groups derived from the 88 items in the food frequency questionnaire

1. White bread	White bread Hard dough, African Bread
2. Brown bread	Brown and wholemeal bread
3. Crisps and savoury snacks	Crackers, cheese biscuits and breadsticks Crisps and savoury snacks
4. Low sugar cereals	Weetabix -porridge/Shredded Wheat
5. Medium & high sugar cereals	>5g/100g of sugar -Cereal bars
6. Boiled and baked potatoes	Boiled and Baked potatoes
7. Fried and roasted potatoes	Chips, waffles and potatoes shapes Roasted potatoes
8. Rice and pasta	Pasta - boiled & tinned Rice - boiled, fried, jollof, rice and peas
9. Chicken and turkey	Chicken and turkey - roasted in batter or breadcrumbs or fried Chicken and turkey - casseroles, curries, African/Caribbean soup
10. Red meat	Beef, pork, lamb and goat - roast meats Beef burgers Beef, pork, lamb and goat - casseroles, curries, African/Caribbean soup
11. Offal	Liver, kidney and faggots
12. Processed meat	Bacon & gammon Ham & processed cold meats Sausages Meat pies, sausage rolls and patties Including McDonalds/burger king
13. Fish	Fish in batter or breadcrumbs Oily fish - fresh and tinned other white fish
14. Quiche and pizza	Quiche and savoury flans Pizza
15. Vegetarian dishes/food	Vegetarian burgers, sausages and nuggets
16. Eggs	Eggs
17. Yam, cassava, plantain	Yam, cassava, fufu, kenkey, green banana, plantain
18. Vegetables	Tinned vegetables Carrots Salad Peas and green beans Tomatoes Cabbage spring greens, spinach, kale and brussels sprouts Broccoli, cauliflower, courgettes and marrow Sweetcorn and mixed veg
19. Root vegetables	Parsnip, turnip, swede and sweet potato
20. Beans and pulses	Baked beans Other beans, lentils and pulses. e.g. chickpeas, black eyed, gunga

21. Cooked and tinned fruit	Tinned fruit Cooked/stewed fruit
22. Fresh fruit	Apples and pears Bananas Oranges, satsumas and grapefruit Plums, cherries and grapes Strawberries, raspberries, mango, kiwi, pineapple and papaya Peaches, nectarines and melon
23. Dried fruit	Dried fruit
24. Nuts	Nuts
25. Cheese and cottage cheese	Cheese Cottage cheese
26. Soup	African/Caribbean fish/shrimp soups Soup - fresh, canned, packet African/Caribbean vegetable soups e.g. Okra, aubergine, tomatoes, spinach African/Caribbean groundnut/peanut soups
27. Sauces and salad dressing	Savoury white sauce Tomato pasta sauce Sauces and salad dressings
28. Yoghurt	Yoghurt and fromage frais
29. Desserts and puddings	Other ready-made desserts in pots Ice-cream other puddings eg. Rice and semolina Ice-lollies Custard and sweet white sauce
30. Cakes and biscuits	Cakes, buns and pastries Chocolate and digestive biscuits Other biscuits
31. Confectionary	Chocolate Sweets
32. Spreads	Marmite and Bovril Peanut butter Butter and margarine
33. Sweet spreads	Jam and sweet spreads
34. Hot drinks	Tea & coffee
35. Milky drinks	Milk and malt drinks
36. Low sugar soft drinks	Low calorie/sugar free squash eg. Robinsons No added sugar Low calorie/diet fizzy drinks
37. High sugar soft drinks	Fruit drinks e.g. Fruit shoots, Rubicon, smoothies Ribena, high juice blackcurrant squash Squash Fizzy drinks
38. Fruit juice	Pure fruit juice
39. Water	Water

2.4.17 Factor analysis

Using the children's average daily frequency (Table 2:9) of the 39 food groups factor analysis with orthogonal varimax rotation was performed to derive the dietary patterns. After the factor analysis was completed the number of factors retained was chosen using the scree plot of eigenvalues (Figure 2:7). Usually the number of data points above the line, before the curve flattens out are the factors which are retained (Costello and Osborne, 2005). The next step in the analyses was rotation of the data. The goal of rotation is to simplify and clarify the data structure, which improves interpretability. Orthogonal rotation was used, so that the factors were uncorrelated, making them easier to interpret. A scoring coefficient cut off was chosen that best characterises the factor. Food groups in a factor with a coefficient ≥ ± 0.22 were chosen (Chapter 5: Table 5:*9*). Foods with a factor loading of ≥ ±0.32 were considered to have a strong association with that factor and the derived dietary pattern labels were selected based on foods which had the highest factor loadings. The coefficients values were selected *a posteriori* so that each dietary pattern had an equal weighting of food groups in each pattern. As the factors have no natural units, they were scaled to standardised z-scores enabling comparison across the generated dietary patterns. A summary of the methodology used to generate the dietary patterns in available in Figure 2:6.

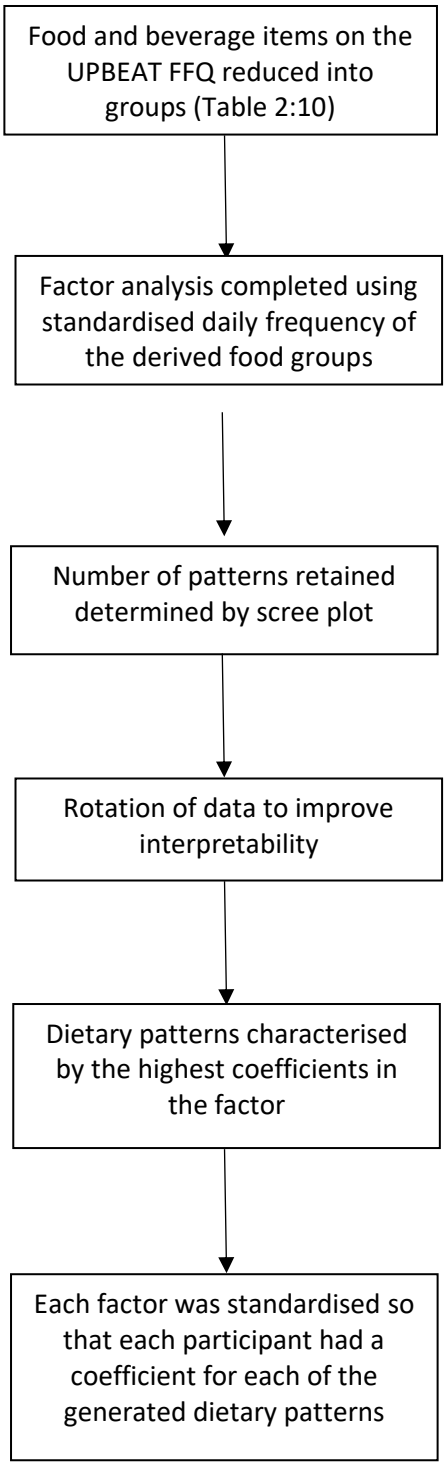


Figure 2:6: Methodology used to derived dietary patterns in the children at 3-years of age

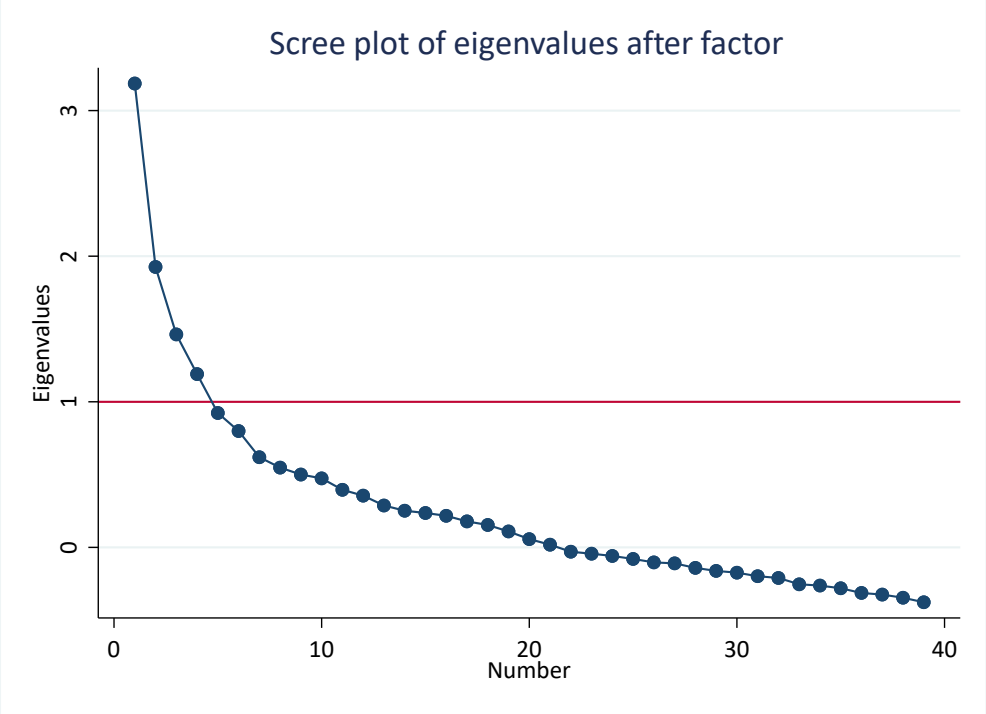


Figure 2:7: Scree plot of eigenvalues to determine factors to retain in the factor analysis

2.4.18 Child Eating Behaviour Questionnaire

The Child Eating Behaviour Questionnaire (CEBQ) (Wardle et al., 2001) is an established inventory to assess children's eating styles. This questionnaire consists of 35 items such as 'My child enjoys tasting new foods' with responses given on a 5-point Likert-type scale (Never=1/ Rarely=2/ Sometimes=3/ Often=4/ Always=5. It measures eight scales: Food responsiveness (5 questions), Emotional over-eating (4 questions), Enjoyment of food (4 questions), Desire to drink (3 questions), Satiety responsiveness (5 questions), Slowness in eating (4 questions), Emotional under-eating (4 questions), and Food fussiness (6 questions). This inventory has been shown to have high internal validity (Wardle et al., 2001). Food approach behaviours include food responsiveness, emotional over-eating, enjoyment of food and desire to drink; food avoidance behaviours were satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness. Higher scores indicate a higher level for the respective eating style.

2.5 **Study design**

In this thesis depending on the research questions and the aim and objective of each of the chapters, different research techniques were used to analysis the data. These include analyses in the context of a randomised controlled trial, cohort analysis and a systematic review.

2.5.1 Systematic review

The systematic review process attempts to collate empirical evidence (qualitative and quantitative) that fit within the pre-defined criteria, which is developed as part of the systematic review protocol. It uses clearly defined systematic methods that are selected with a view to minimizing bias, therefore providing more reliable findings from which conclusions can be drawn and decisions made (Antman et al., 1992). Within this thesis the systematic review process was used in chapter three.

2.5.2 Randomised controlled trial

Randomised controlled trials are regarded the gold standard for establishing causal associations. RCTs are a form of experimental design in which participants being tested are randomly allocated to different interventions, the groups are balanced in both known and unknown demographic factors. Within a well-designed study, randomisation ensures that imbalance between the intervention and control groups at baseline is purely due to chance and reduces selection and allocation bias, which are known limitations of observational data. Balancing the groups and minimising for known characteristics in the intervention limits potential confounding of data (Richmond et al., 2014). Therefore, if a significant difference occurs for an outcome of interest the effect is likely to be due to the intervention.

2.5.3 Cohort studies

Cohort studies typically include participants within a population or group over a set time period and therefore are less prone to selection bias in comparison to other study designs, such as case-control or retrospective study designs. Although the internal validity of cohort studies is weak, due to the strong potential for confounding, the external validity is thought to be higher, and cohort studies with detailed data collection are able to adjust for potential confounding variables and therefore inform on associations between exposure and outcomes variables.

2.5.4 Sample size

For the main trial the sample size calculation estimated that 1,546 women needed to be recruited (allowing for 20% drop-out) to give 80% power to detect a reduction in the primary outcomes; a 25% in the incidence of GDM and 30% in rates of delivery of large for gestational age infants. These figures were based on the findings of the pilot study (Poston et al., 2013), a total of 1,555 women were recruited to the UPBEAT trial.

For the data presented in this thesis an intention to treat analysis was completed for all participating mothers and children in both the intervention and the control arm. The sample size was determined on the available data from the original cohort of 1,555 mother- child dyads. There was no possibility of increasing the sample size; and no advantage to be gained by reducing it. With data available for 514 children, this provided the power to detect differences and limit the influence of extremes or outliers. With 250 children in each treatment arm, and assuming a SD of 1 the power is 91.6% to detect a clinically important difference of 1/3 of a SD in the Z-score for subscapular skinfold (based on the WHO standards).

2.6 **Statistical analyses**

2.6.1 Data management

The distribution of continuous data was checked by describing the variable (mean, standard deviation, median and IQR) and plotting histograms to identify the distribution and potential incorrect data points (methodology described in Figure 2:8). If the data was positively skewed the variable was log-transformed for the analysis, unless otherwise stated. To identify outliers and incorrect values, variables were standardised and data points ±≥4 standard deviations from the mean were checked for data entry and measurement errors. If a data point was thought to be a true outlier it was not removed, for example the mean weight of the children at three years of age was 17.1 kg with a range of 10.8 – 35.9kg. It was assumed that the 35.9kg was an incorrect value, however, after consultation with the research midwife who completed the data collection, they confirmed that it was an outlier and not an incorrect value, therefore the variable was not dropped from the analysis.

2.6.2 Summary statistics

Binary and categorical demographic variables were summarised as percent and number, the depending on the distribution of continuous variables these were summarised as mean ± standard deviation or median and interquartile range as appropriate.

2.6.3 Metabolomic analysis

A total of 158 metabolic features were measured and quantified using a Nuclear Magnetic Resonance targeted platform (www.computationalmedicine.fi) including 129 lipid measures (lipoprotein particle subclasses, particle size, cholesterols, fatty acids and apolipoproteins), nine glycerides and phospholipids, and 20 low-molecular weight metabolites including branched-chain and aromatic amino acids, glycolysis-related markers, and ketone bodies (Appendix 3). All metabolites were standardised to z-scores so that for each variable the mean score was zero and the data was converted to standard deviations from the mean (z-scores). For the purpose of this analysis the data was presented as the effect of the intervention on rate of change in metabolites in SD units from baseline to 34^{+0} to 36^{+6} weeks gestation, compared to the control group for each of the reported metabolites.

2.6.4 Unadjusted analyses (simple regression)

Prior to multiple regression, unadjusted analyses were completed to assess for associations between exposure and outcome variables. If the outcome of interest was binary or categorical the chi-square test was used. Mann-Whitney U tests or t-test were undertaken for continuous data depending on the distribution.

2.6.5 Adjusted analyses (multiple regression)

Regression analyses were used to determine the relationship between exposure and the outcome of interest, with adjustment for confounding variables. Linear, quantile and logistic regression were used to estimate the relationship between exposures and continuous or binary outcomes. Regression analyses generate an equation of the line of best fit through the observed data:

Box 2.5 Summary of the data required to generate a line of best fit

y is the outcome of interest *a* is the intercept *x* is the exposure variable *b* is the gradient of the line The gradient of the line, also known as the regression coefficient (beta), for each unit change in the exposure variable the regression coefficient is the change in the outcome variable.

There are several assumptions when using regression analysis, these include:

1) The distribution of the residuals is normal

2) The relationship is linear, and the standard deviation of the outcome is constant at all values of the exposure, therefore there is no heteroscedasticity and the residuals (distance from the generated line of best fit).

The regression coefficient is an estimated parameter in a statistical model, that expresses the strength of the relationship in an analysis, there is an example summarised in Figure 2:9 for children's BMI z-score which details the process for analysing data using regression. The coefficient will have a different meaning depending on the outcome of interest as linear and quantile regression generate a continuous variable whereas logistic regression generates a proportion (odds ratio). For all analyses a 2-sided p-value with a statistical significance set as $p<0.05$ was used throughout for rejection of the null hypothesis. All data were analysed using Stata software, version 15.0 (StataCorp, College Station, Texas).

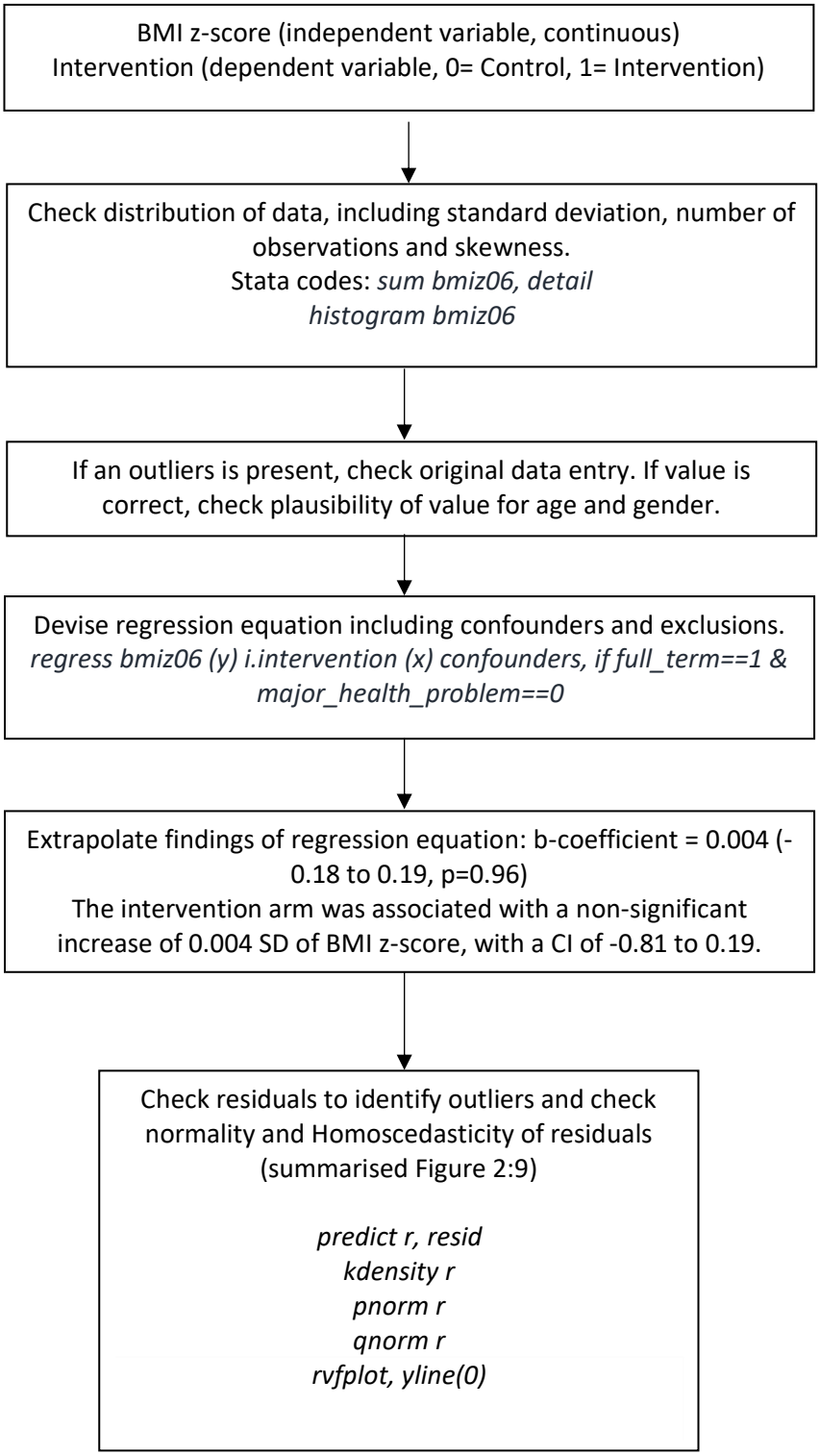


Figure 2:8: Flowchart of data analysis

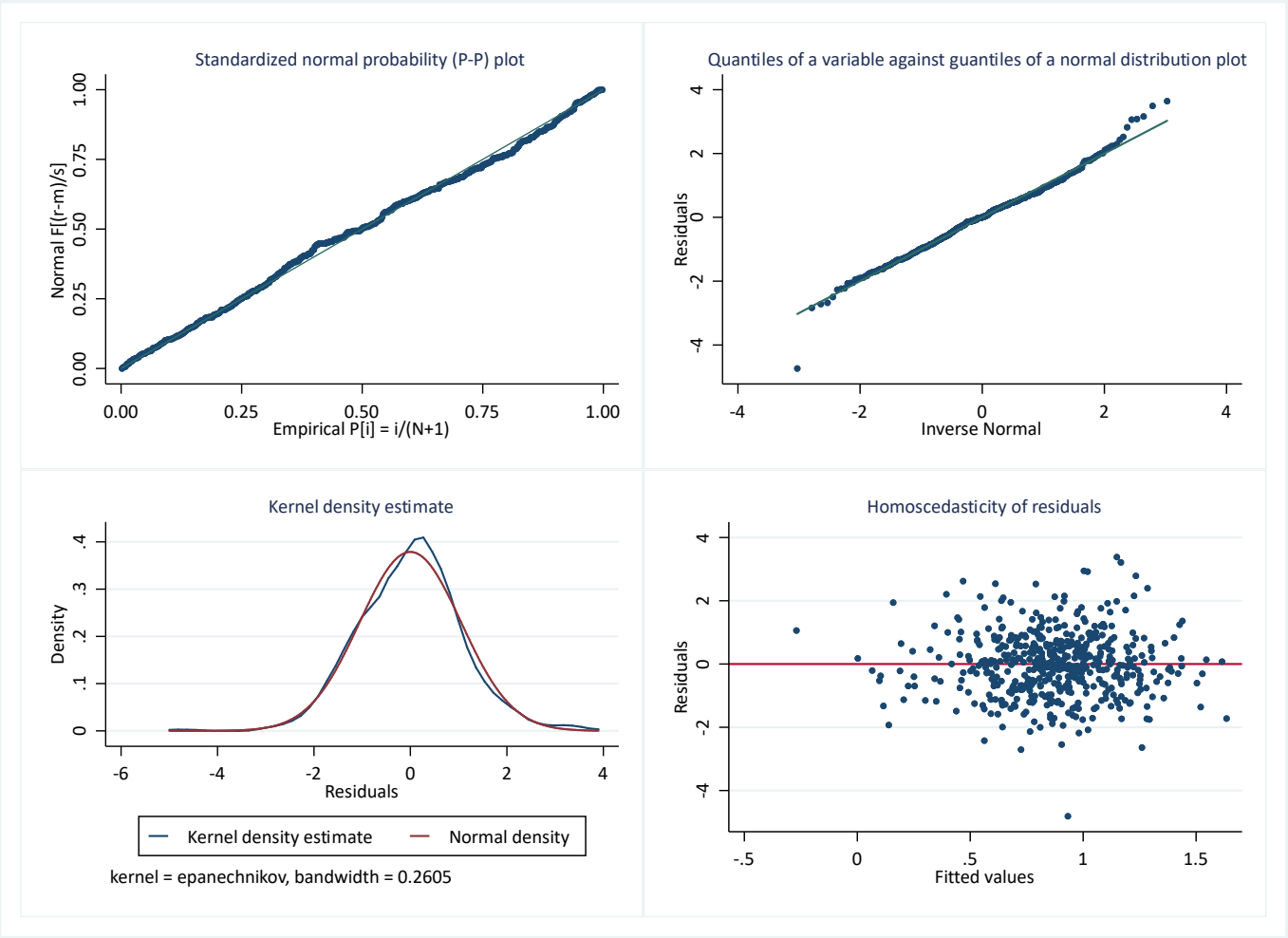


Figure 2:9 Diagnostic graphs for regression analyses

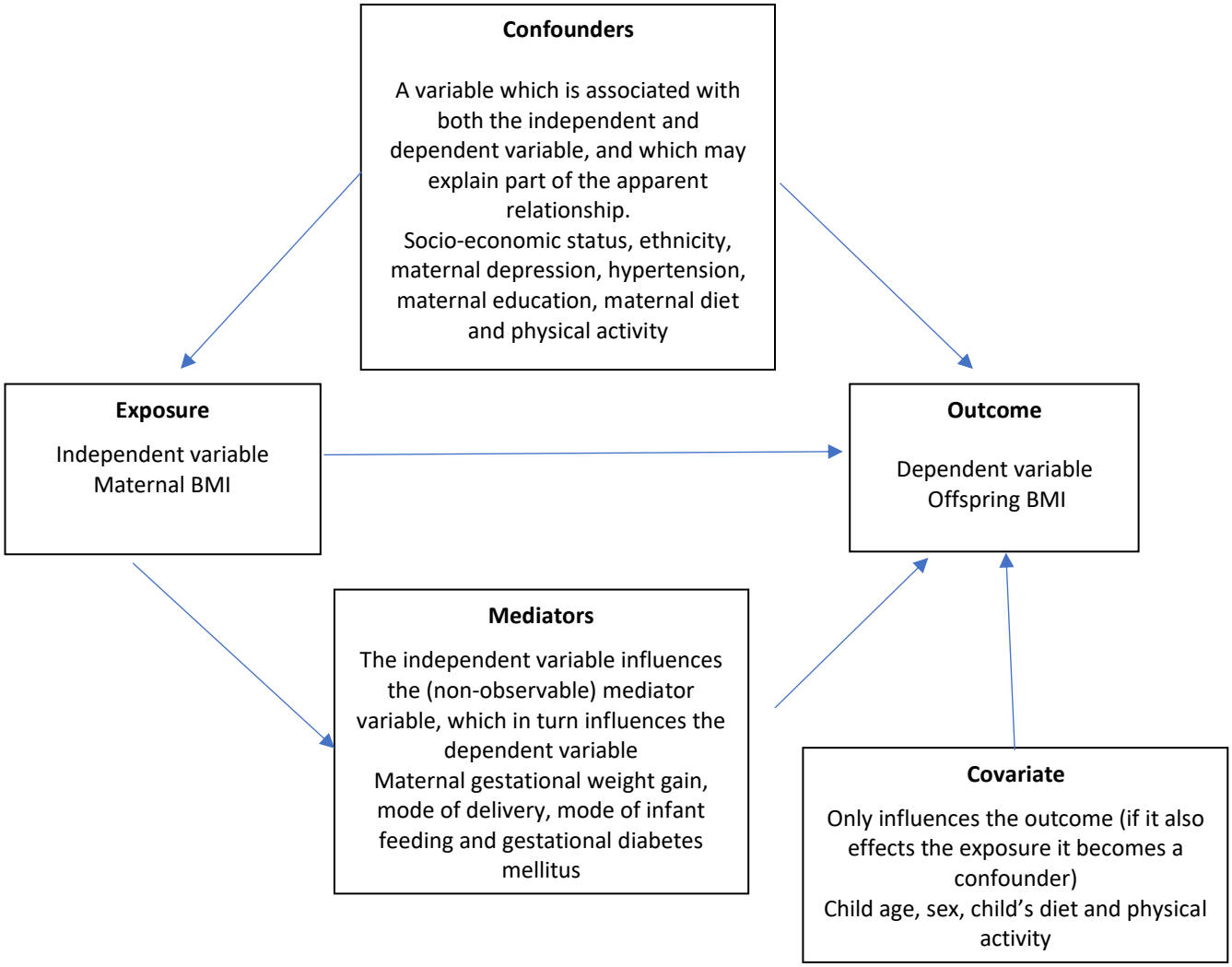


Figure 2:10 Example of the interaction of confounding variables on a multiple linear regression analysis

2.6.6 Confounder selection

Confounders were selected *a-priori* using relevant clinical knowledge. Confounders chosen for each analysis and explanation of selection and type of variable are described in the individual chapters. Depending on the confounding variable these were treated as either continuous, categorical or binary or a combination of all three. For example, a selection of maternal confounders recorded at baseline are reported in Table 2:11.

Table 2:11 Examples of confounding variables and description of type of data

Variable	Type of variable	Description
Maternal age (years)	Continuous	Total number of years
Parity	Binary	Nulliparous vs multiparous
Education attainment (years)	Binary and continuous	≤11 years vs > 11 years of full-time education Total number of years.
Ethnicity	Categorical	White vs Black vs Asian vs Other
Maternal smoking	Binary and categorical	Current smoker vs. non-smoker current Smoker in early pregnancy vs gave up smoking in early pregnancy vs ex-smoker vs non-smoker (reference)
Socioeconomic status, assessed by Index of Multiple Deprivation Quantiles	Categorical	Quintiles 1 (least deprived) vs 2 vs 3 vs 4 vs 5 (reference, most deprived)
Maternal pre-pregnancy BMI	Continuous and categorical	Total BMI Obesity classes: I (reference) vs II vs III.

2.6.7 Missing data

Missing data is defined as values that are not available and that would be meaningful for analysis if they were observed. It is particularly challenging and common within RCTs as attrition is a notable weakness in this type of study design (White et al., 2011). For the purpose of this thesis, missing data was defined as variables which we planned to be collect but were unable to do so. The presence of missing data has three important implications for the analyses presented in this thesis and are summarised in box 2.6.

Box 2.6 Implications of missing data

1. Missing data can introduce bias, potentially leading to misleading inferences regarding to changes within a mean difference.

2. Missing data in longitudinal studies tends to be spread sporadically over many subjects and depending on how highly correlated the missing data is in comparison to the observed data, there may potentially be a loss of precision and power.

3. Missing data may be unbalanced between the two arms within a randomised controlled trial setting.

Selection of statistical analyses can take into account missing data, however the nature and pattern of missingness needs to be understood as this can result in biases. For the purpose of this thesis, review of methods of data collection, preparation and analysis were undertaken to highlight the issues and mechanisms of missing data.

2.6.8 Strategies to deal with missing data

Missing data is common within all randomised controlled trials. Within the UPBEAT study, a strategy was devised to deal with missing covariates and outcomes of interest as described below.

2.6.9 Missing data at baseline

Any pregnant woman within the UPBEAT study with any baseline measure, who was randomised, was defined as a participant. As there was minimal data missing at baseline, it was assumed that any imbalance observed within the baseline data was due to chance.

Box 2.7 Types of missing data

Missing Completely At Random (MCAR): Refers to the situation when the probability of missingness is completely unrelated (independent) of all the variables (irrespective of whether some of them may later be used as outcomes or covariates in an analysis model). MCAR refers to data where complete cases are representative of the original sample therefore associations or conclusions based on these complete cases are thought to be applicable to the larger population or study group.

Missing At Random (MAR): MAR refers to a situation where the probability of data being missing is not associated or dependent on the unobserved observations but shares relation to the observed data, i.e. the pattern of missing data is conditional on another variable.

Missing Not At Random (MNAR): Data are missing dependent on unobserved data, therefore cannot be ignored. One of the main limitations of MNAR is that estimates and potential associations derived may be biased.

2.6.10 Missing data at follow-up

Missing data following randomisation was assumed as lost to follow-up. A framework was devised for dealing with incomplete observations, and has been utilised for also previous UPBEAT analyses, allowing the correct statistical method to be chosen and subsequently implemented (White et al., 2011), as described below:

1. Attempt to follow up all randomised participants, even if they withdraw from allocated treatment.
2. Perform a main analysis of all observed data as a complete case analysis
3. Check the proportion of missing data between the intervention and the control arms.
4. Perform sensitivity analyses, where appropriate, to explore the mechanism of the missing data summarised in box 2.7.
5. Account for all randomised participants, at least within sensitivity analyses, therefore analysing the statistical difference in the women who returned to the follow-up and those who did not.
6. Complete multiple imputation as this allows individuals with incomplete data (missing from 3-year follow-up) to be included in a sensitivity analysis. The multivariate imputation assumes missing at random (MAR) and can also increase statistical power and enables exploration of whether loss to follow-up resulted in type-2 statistical errors.

2.6.11 Complete case analysis

Complete case analysis was used in chapters four-six, but it assumes that any missing data is MCAR. Therefore, if and outcome of interest is missing for a participant they are not included in the analysis. However, this method can result in loss of statistical power, and if substantial may result in biased results due partial loss of data. Within longitudinal analyses, such as the UPBEAT study allocation groups missing data is likely to have different demographic characteristics in comparison to those with complete data, for example multiparous women may be less likely to return due to family constraints. However, inclusion of these demographic differing variables (included vs excluded) within the regression model as a confounding variable the risk bias is likely to be reduced (Graham and Donaldson, 1993). This approach was utilised throughout the UPBEAT results chapters.

Chapter 3 : Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature.

Publications based on this chapter:

Dalrymple KV, Martyni-Orenowicz J and Flynn AC, Poston L and O'Keeffe M. Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature. *Matern Child Nutr*. 2018. 14(4): e12628

3.1 Abstract

Background: Evidence suggests that adverse nutritional exposures during in utero development may contribute to heightened risk of obesity in childhood. Pregnancy offers the opportunity to modify the intrauterine environment by manipulation of diet and/or physical activity, which may result in favourable health benefits for the child.

Objective: The objective of this systematic review was to determine whether antenatal lifestyle interventions in pregnant women, aimed at modifying diet and/or physical activity, lead to a reduction in measures of offspring obesity in early childhood.

Methods: Three electronic databases were searched from January 1990 to July 2017 for antenatal interventions with subsequent offspring follow-up publications.

Results: Eight trials were identified. Five trials included women from all body mass index (BMI) categories, three trials included obese women only. Children in the offspring follow-up studies were aged 6 months to 7 years. Measures of adiposity in the offspring (n=1989) included weight, BMI, z-scores, circumferences and skinfold thicknesses. Two studies, focusing on obese women only, reported reduced measures of adiposity (subscapular skinfold thickness and weight-for-age z-score) at 6 and 12 months, respectively. The remaining six studies, two from infancy and four in early childhood found no effect on measures of adiposity.

Conclusion: Measures of obesity up to 12 months of age have been shown to be reduced by antenatal lifestyle interventions during pregnancy in obese women. Due to the heterogeneity of the methodology of the antenatal interventions and the reported offspring outcomes we were unable to draw any conclusion on the influence of antenatal interventions on measures of obesity in early childhood.

3.2 Introduction

The World Health Organisation (WHO) have stated that childhood obesity is one of the most serious global public health challenges for the 21st century (World Health Organisation, 2016). In the United Kingdom, 24.4% of children aged between two and five years are classified as overweight or obese (van Jaarsveld and Gulliford, 2015). Prevalence rates are also increasing in countries undergoing economic transition where they face the burden of both under and over nutrition (GBD Obesity Collaborators, 2017).

A concerning implication of obesity in children is that once it is established it is difficult to rectify as it tracks into adulthood (Singh et al., 2008). Modelling of growth trajectories from childhood has suggested that the majority of children in the USA (57%) will be obese by the age of 35 (Ward et al., 2017), with half of this projection being established in childhood. However, a recent longitudinal analysis of over 62,000 men living in Denmark suggested that the adverse long-term health effects of childhood overweight can be reversed if weight is normalised prior to puberty (Bjerregaard et al., 2018).

Childhood obesity is a multifactorial condition in which dietary (Ebbeling et al., 2002), environmental (Tremblay and Willms, 2003) and genetic (Aguilera et al., 2013) factors can all play a role. Identification of risk factors and appropriate interventions for the prevention and management of childhood obesity are therefore considered critically important and prevention is a public health priority for countries across the world. There is also a growing body of evidence which suggests that childhood obesity is programmed through exposures during *in utero* development, such as maternal under (Painter et al., 2005) or over-nutrition (Lawlor et al., 2012; Yu et al., 2013) gestational diabetes (GDM) (Ruchat et al., 2013) and excessive gestational weight gain (GWG) (Castillo et al., 2015). It is hypothesised that the in utero environment influences critical periods of developmental plasticity resulting in lifelong effects on the offspring and may programme obesity in the child (Gaillard et al., 2016b; Godfrey et al., 2016).

Given the evidence for developmental programming of obesity, antenatal interventions are increasingly utilised as a strategy to prevent childhood obesity. An individual participant meta-analysis of 36 randomised controlled trials (RCTs) recently concluded that diet and physical activity interventions in weight heterogeneous pregnant women can reduce GWG and showed modest improvement in clinical outcomes for both the mother and infant (i-WIP

Collaborative Group, 2017). Further, a systematic review which assessed childhood obesity interventions initiated in the first 1000 days of life found that 35% of early life interventions improved childhood weight status, and interventions with the greatest preventive effect should be initiated early in life (Blake-Lamb et al., 2016). Of the studies identified only two studies explored interventions initiated during pregnancy; neither of which had an effect on childhood weight. The current review seeks to expand on this finding by systematically evaluating the impact of dietary and/or physical activity interventions, targeted specifically to the antenatal period, on offspring measures of adiposity in early childhood excluding neonatal measures which reflect directly *in utero* exposures. The review also attempts to define associations between offspring adiposity and 1) the characteristics of the dietary and/or physical activity intervention tested; 2) the method of intervention delivery; 3) the effect of the antenatal intervention on maternal and neonatal outcomes.

3.3 Methods

This systematic review was conducted in accordance with the relevant criteria of the PRISMA guidelines for reporting a systematic review (Moher et al., 2009).

Table 3:1: Summary of PICOS criteria for the inclusion of follow-up studies from antenatal dietary and lifestyle interventions

Parameter	Description
Population	Pregnant women, >16 years, with detailed pre-pregnancy or first trimester body mass index data
Intervention	Diet and/or physical activity
Comparison	Standard antenatal care
Outcomes	Offspring body composition measures from 6 months – 7 years of age
Study design	Randomised controlled trials

3.3.1 Literature search

Three databases were searched for relevant articles, Medline, Embase and Cochrane Central Register of Controlled Trials. The search terms are available in Appendix 2, they were adapted for different databases and were limited from 1st January 1990 – 4th July 2017. The Institute of Medicine guidelines (now known as the National Academy for Medicine) regarding GWG thresholds were published in 1990, therefore only studies published after 1990 were included in the electronic search to ensure the included publications contained up-to-date knowledge regarding maternal GWG. Reference lists in identified articles, articles cited in relevant reports and review articles were hand searched to identify any additional relevant studies.

3.3.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed using the PICOS (population, intervention, comparison, outcomes and study design) approach summarised in Table 3:1. Studies were included if they specified: 1) offspring follow-up studies from antenatal RCTs with diet and/or physical activity interventions initiated no later than the second trimester; 2) antenatal RCTs with dietary and/or physical activity intervention in pregnant women with reported BMI and maternal age >15 years according to United Nations classification for women of reproductive age (UNFPA, 2016); 3) offspring follow-up studies which included measures of body composition, including body mass index (BMI), body fat percentage and circumferences; 4) if the age of the offspring at follow-up was between 6 months and 8 years,

which is the limit of early childhood as defined by UNESCO (UNESCO, 2016). For each identified offspring follow-up study the original maternal RCT on which it was based was also analysed for intervention design and outcomes. Antenatal studies were excluded if they were: non-randomised trials, observational studies and cohort analyses of offspring outcomes, studies which included multiple pregnancies. Both follow-up and antenatal studies not published in English were also excluded.

3.3.3 Study selection and data extraction

Following removal of duplicates, titles and abstracts were independently screened against inclusion criteria by two researchers, n=3406 papers were excluded at this stage. The database search identified three maternal lifestyle intervention RCTs which had not yet published follow-up data on their offspring. The authors of these three articles were contacted and the studies were subsequently excluded (Bogaerts et al., 2013; Renault et al., 2014; Thomson et al., 2014). Fifteen studies were assessed for eligibility and the full-text articles were retrieved. Seven studies were excluded with details reported in Figure 3:1. Data extraction was completed separately and systematically by the same two reviewers and included general characteristics: title, authors, date and place of publication; offspring follow-up: number, method of data collection, measures of obesity, age at follow-up; risk of bias: process of randomisation selection and allocation, loss to follow-up; maternal lifestyle intervention: number and BMI of participant mothers, location, setting, description of intervention (type, duration, frequency).

3.3.4 Data synthesis

For this review the data was synthesised qualitatively, through a narrative summary technique to aid interpretation of trial results. Due to the heterogeneity of the anthropometric measurements used to assess adiposity in the offspring a meta-analysis was precluded. The trials were divided into two groups according to pre-pregnancy BMI data; 1) trials which included women of all categories of BMI (underweight, normal, overweight and obese) and 2) trials in obese women only. As there is a known association between pre-pregnancy BMI and the development of childhood obesity, by separating the trials by BMI classification this association could be investigated.

3.3.5 Study assessment

The Cochrane Handbook for Systematic Reviews of Interventions tool (Higgins and Green, 2011) was used to assess the validity and bias of each offspring follow-up publication included. The domains used in this systematic review include: randomisation selection (selection bias), allocation concealment (selection bias) and follow-up of participant drop-out from recruitment to termination of study (attrition bias). Performance bias was not included in the bias assessment due to the nature of the interventions provided. The studies were ranked using high, moderate and low risks of bias, and an overall risk was subsequently determined.

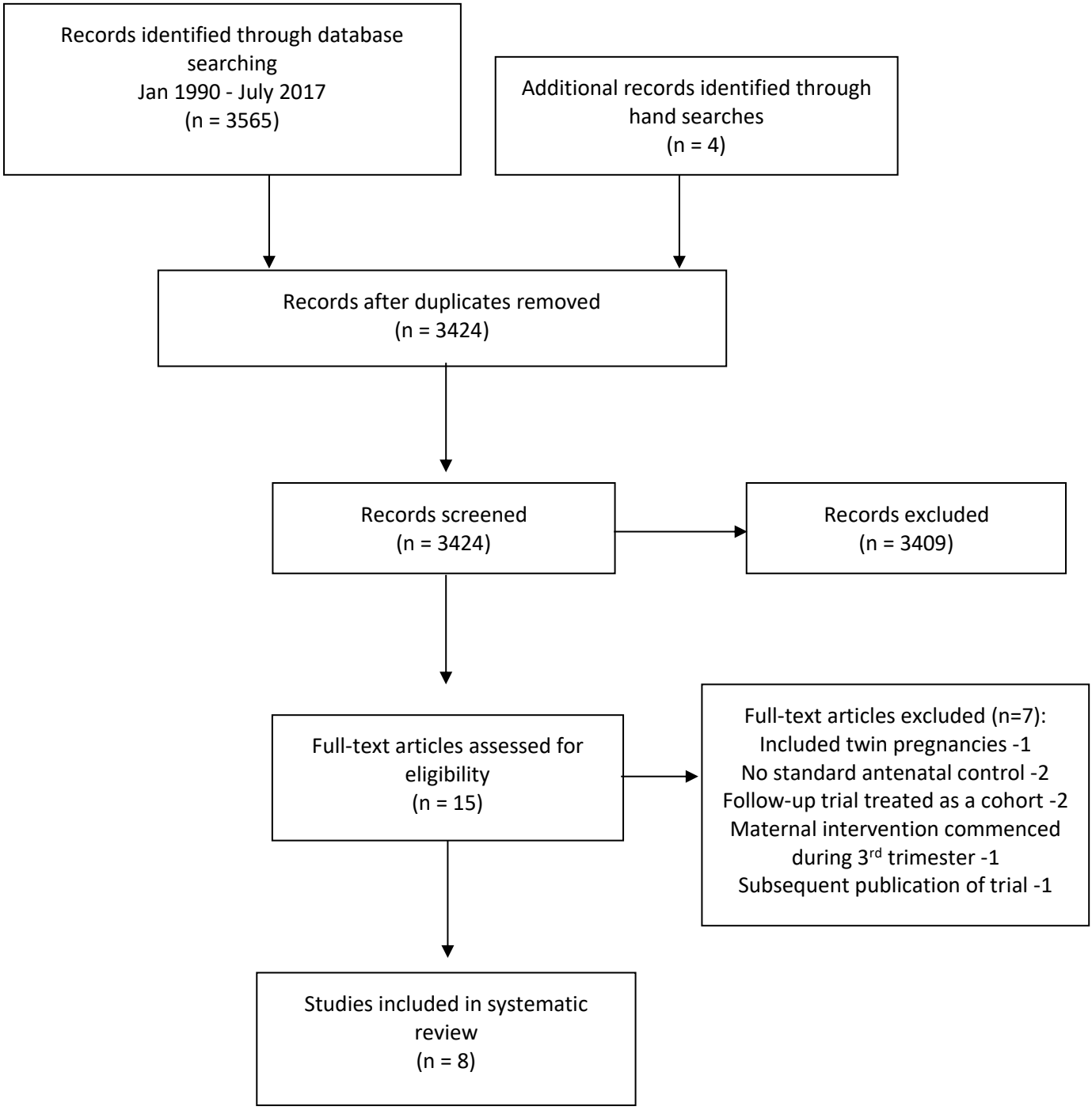


Figure 3:1: Flowchart of study selection in accordance with PRISMA guidance

3.4 Results

The study identification and selection process for the offspring follow-up studies is presented in Figure 3:1. A total of 3565 titles were identified in the initial search (Medline 2967, Embase 218, Cochrane 380). Following screening of titles and abstracts, 15 studies were fully assessed for eligibility of which eight met the inclusion criteria. Predominant reasons for exclusion included RCTs that were ongoing and lack of offspring follow-up publications.

The characteristics for the offspring follow-up are summarised in Table 3:2. Offspring data was collected from a total of 1,989 children, representing 35% to 88% of the offspring available from the antenatal RCTs. The number of offspring investigated from the antenatal studies ranged from 72 to 698. Offspring age at follow-up was 6 months (Horan et al., 2016; Patel et al., 2017a) 1 year (Rauh et al., 2015; Vesco et al., 2016), 2.8 years (Tanvig et al., 2014), 4-5 years (Mustila et al., 2012; Ronnberg et al., 2017) and 7 years (Kolu et al., 2016). The measures of adiposity recorded are described in Table 3:2, and included anthropometric measurements of weight, height, BMI, circumferences (mid-upper arm, abdominal, hip, thigh), skinfold thicknesses and estimated total body composition values via dual-energy x-ray absorptiometry (DXA) scans.

3.4.1 Offspring measures of adiposity

When reported, anthropometric measures were converted to z-scores and adjusted for infant sex, age and length and standard deviations using WHO growth standards (Mustila et al., 2012; Tanvig et al., 2014; Horan et al., 2016; Vesco et al., 2016; Patel et al., 2017a; Ronnberg et al., 2017). One study (Kolu et al., 2016) calculated the children's BMI using a Finnish BMI for age calculator for children aged 2–20 years (Saari et al., 2011). Sums and ratios of anthropometric characteristics as opposed to individual measures were also used to estimate infant adiposity (Horan et al., 2016; Vesco et al., 2016; Patel et al., 2017a). Two trials utilised weight changes over time, obtained from multiple measurements to create growth trajectories from birth to 12-months (Rauh et al., 2015). and 2-years (Mustila et al., 2012) of age. One study (Tanvig et al., 2014) used DXA scans to obtain body composition values from the children, which were completed for <50% of the study population.

Table 3:2: Offspring follow up of children born to mothers whom received an antenatal lifestyle intervention

Antenatal study	Follow-up study	Follow-up participants (% of antenatal sample)	Age of children at follow-up	Anthropometric outcomes	Breastfeeding rates between control and intervention arm
All BMI categories					
Walsh et al (2012)	Horan et al. (2014)	n=280 (35%)	29 ± 13.14 weeks	Anthropometric measurements recorded in both follow-ups: weight, length, circumferences (MUA, abdominal, hip and thigh), skinfold data (subscapular, triceps, biceps and thigh).	Not reported
Rauh et al. (2013)	Rauh et al. (2015)	N=220 (88%)	6^{th}-7^{th} month & 10^{th}-12^{th} month	Weight, recorded by paediatrician in an infant health record.	No significant difference
Kinnunen et al. (2007)	Mustila et al. (2012)	n= 72 (66%)	0-48 months	Weight development of the offspring: weight-for-length z score (0-48 months), BMI z-score (24-48 months).	No significant difference
Ronnberg et al. (2014)	Ronnberg et al. (2017)	N=300 (80.2%)	5 years	BMI and BMI z-scores.	No significant difference
Luoto et al. (2011)	Kolu et al. (2016)	n=173 (43.4%)	7 years	BMI*.	Not reported
Obese only (BMI ≥30 kg/m^2)					
Poston et al. (2015)	Patel et al. (2017)	n=698 (45.9%)	4-8 months	Infant skinfold data (subscapular and triceps), weight, length, abdominal and MUA circumferences. WHO growth standards were used to convert the infant measurements to z-scores which were adjusted for infant age and gender. Estimated total body fat percentage was calculated using skinfold measurements.	No significant difference
Vesco et al. (2014)	Vesco et al. (2016)	n=89 (78%)	12 ± 3 months postpartum	Weight, length, skinfold data (triceps and subscapular) and z-scores	Not reported
Vinter et al. (2011)	Tanvig et al. (2015)	n=157 (52.2%)	2.5-3.2 years	Abdominal circumference, weight and height, skinfold thickness data (triceps and subscapular) and DXA. BMI Z-scores were adjusted for age and sex-specific Danish standards.	No significant difference

*Abbreviations: BMI, body mass index; DXA, Dual Energy X-ray; MUA, mid-upper arm; SD, standard deviation; WHO, World Health Organisation. * Children's BMI were calculated using a Finnish BMI for age calculator for children aged 2–20 years* (Saari et al., 2011).

3.4.2 Effect of interventions on offspring adiposity

Table 3:3 shows the effectiveness of lifestyle interventions on offspring anthropometric measures at follow-up. Two RCTs, including obese women only reported significant reductions in offspring measurements of adiposity (subscapular skinfold thickness (Patel et al., 2017a) and weight-for-age z-score (Vesco et al., 2016) between the control and intervention groups. The two trials involved modifying diet and physical activity and both demonstrated a significant reduction in GWG in the intervention arm. In Horan et al. participants were recruited on the basis of previous delivery of a large for gestational age (LGA) infant, no significant differences were found in measures of obesity in infants in the intervention arm at 6 months of age compared to the control arm. However, when the data was analysed as a cohort using multiple linear regression modelling, associations between specific maternal dietary variables and infant adiposity, GI, saturated fat and sodium intake in pregnancy were associated with some measures of offspring adiposity at follow-up including weight-for-age z-score, BMI-for-age z-score and select skinfold measurements.(Kolu et al., 2016) Kolu et al. conducted a separate statistical analysis of a subset that included data obtained from children of women adherent to the lifestyle intervention in the NELLI trial, which included women from all BMI categories. When this subset was analysed, summarised in Table 3:3, there was a significant reduction in childhood BMI between the intervention and control groups at 7 years of age (n=24, I: 20.5 kg/m^2 vs C: 22.5 kg/m^2, p = 0.04).

3.4.3 Antenatal studies

Characteristics of the eight antenatal interventional studies included are summarised in Table 3:4. The total sample size for the antenatal interventions was 3,988, which varied by study from 118 to 1,555. All interventions were conducted in high-income countries; Denmark (Vinter et al., 2011), Finland (Kinnunen et al., 2007; Luoto et al., 2011), Germany (Rauh et al., 2013), Ireland (Walsh et al., 2012), Sweden (Ronnberg et al., 2015), UK (Poston et al., 2015) and USA (Vesco et al., 2014). Six trials included a combined dietary and physical activity intervention approach. Walsh et al. (Walsh et al., 2012) included a diet-only intervention and Ronnberg et al. included a physical activity only intervention. The study designs included five RCTs (Vinter et al., 2011; Walsh et al., 2012; Vesco et al., 2014; Poston et al., 2015; Ronnberg et al., 2015), two cluster-RCT (Luoto et al., 2011; Rauh et al., 2013) and one quasi-RCT (Kinnunen et al., 2007). Five trials included women from all BMI categories (Kinnunen et al., 2007; Luoto et al., 2011; Walsh et al., 2012; Rauh et al., 2013;

Ronnberg et al., 2015) (underweight to obese, these trials did not analyse their results depending on pre-pregnancy BMI), and three included obese women only (BMI ≥30 kg/m^2) (Vinter et al., 2011; Vesco et al., 2014; Poston et al., 2015).

Table 3:3: Impact of antenatal lifestyle intervention on offspring adiposity at follow-up

Antenatal study	Follow-up	Childhood outcomes	Additional results
All BMI categories			
Walsh et al (2012)	Horan et al. (2016)	At 6 months, no difference in any of the infant anthropometric measured between the C and I groups. Including BMI, SFT, z-scores and circumferences	Associations were observed between maternal dietary intake and GI during pregnancy and offspring adiposity at 6 months of age.
Rauh et al. (2013)	Rauh et al. (2015)	After adjustments no difference in weight at follow-up at 10-12 months of age C:9736g ± 999 vs I:9382g ± 931, p = 0.099.	Among women receiving lifestyle counselling, only 8% retained more than 5 kg, while 17% in the control group retained >5 kg. For the whole cohort, an association between higher GWG and increased 12-month weight retention was found (0.4 kg weight retention per 1 kg increase in GWG, p<0.001).
Kinnunen et al. (2007)	Mustila et al. (2012)	The antenatal lifestyle intervention did not reduce weight gain among the offspring (95% CI-0.025 to 0.009, p=0.34).	
Ronnberg et al. (2014)	Ronnberg et al. (2017)	No difference in mean BMI z-scores at age 5, C: 0.26 vs I:0.34, p=0.510.	Maternal obesity was an independent risk factor for offspring obesity at age 5 (OR=4.81, p=0.006).
Luoto et al. (2011)	Kolu et al. (2016)	No difference in BMI* of children at 7 years (C: 22.5kg/m^2 vs I: 21.3kg/m^2, p = 0.07).	For children with mothers classified in the adherent group (AG) BMI* was lower (n=24, C: 22.5 kg/m^2 vs I: 20.5 kg/m^2, p = 0.04). AG: during pregnancy mothers fulfilled at least 3/5 dietary aims and/or their self-reported PA exceeded 800 MET/mins per week and their BMI did not exceed their BMI specific limits).
Obese only (BMI ≥30 kg/m^2)			
Poston et al. (2015)	Patel et al. (2017)	Subscapular skinfold thickness z-score was 0.26 SDs (-0.49 to -0.02) lower in the intervention arm (p=0.031). Infants in the intervention arm had a 5% lower subscapular skinfold thickness (mm) (p=0.021)	Causal mediation analysis suggested that lower infant subscapular skinfold thickness was mediated by changes in antenatal maternal diet and GWG rather than postnatal diet. Maternal dietary GL (p<0.001) and SFA (p<0.001) intake were reduced in the intervention arm at 6 months postpartum.
Vesco et al. (2014)	Vesco et al. (2016)	There was a significant main effect of group for infant weight-for-age z-scores (b=-0.40, 95% CI: -0.75 to -0.05; p=0.024)	There was a difference in the adjusted change for weight (kg): -0.20 (95% CI: -0.38 to -0.02; p=0.031) in the children from the intervention arm.
Vinter et al. (2011)	Tanvig et al. (2015)	No difference in randomised group mean: BMI Z-score (C: -0.18 [-0.42;0.05] vs I: 0.06 [-0.17; 0.29]). Percentage of ow or ob children (10.9% vs 6.7%)	The non-significant result may reflect the limited difference in GWG between intervention and control groups

*Abbreviations: BMI, body mass index; C, control; CI, confidence interval; GDM, gestational diabetes mellitus; GI, glycaemic index; GL, glycaemic load; GWG, gestational weight gain; I, intervention; MET, metabolic equivalent of task; MUA, mid-upper arm; ob, obese; ow, overweight; PA, physical activity; SD, standard deviation; SFA, saturated fatty acids. *Children's BMI were calculated using a Finnish BMI for age calculator for children aged 2–20 years (Saari et al. 2011).*

Table 3:4: Characteristics of the antenatal interventions

Reference	Country/ Design	Aims	Outcomes	Study population	Intervention
All BMI Categories					
Walsh et al. (2012) ROLO study	*Ireland* RCT	To determine if a low GI diet from early pregnancy in a group of women all in their second pregnancies who had previously delivered an infant weighing greater than 4000g.	Primary infant outcome: birth weight. Secondary outcomes: GWG and maternal glucose intolerance.	N = 781 all BMI categories I: n=383 BM I= 26.8 ± 5.1 kg/m^2 C: n=398 BMI=26.8 ± 4.8 kg/m^2 No published ethnicity data	I: Diet only. 1 group dietary session at <18 weeks' gestation. Introduced to principles of study, rationale of low GI diet in pregnancy and provided with written resources for swapping to low GI foods. Further meeting with dietitian to reinforce the low GI diet concept at 28- and 34-weeks' gestation. C: Standard antenatal care.
Rauh et al. (2013) FeLIPO study	*Germany* Cluster-RCT	To determine if counselling, focusing on diet, physical activity and weight monitoring prevents weight gain in excess of IOM guidelines.	Primary maternal outcome: GWG within IOM guidelines.	N=250 all BMI categories I: n=167 BMI: 19.9-23.7 kg/m^2 C: n=83 BMI: 20.6-26.6 kg/m^2 No published ethnicity data	I: Diet and physical activity. Recruited <18week gestation. Two individual counselling sessions in the 20th and 30th week of pregnancy, including nutrition PA and GWG monitoring and personalised feedback on their 7-day food and activity diaries. C: Standard antenatal care.
Kinnunen et al. (2007)	*Finland* Quasi-RCT	To determine if individual counselling on diet and physical activity during pregnancy can prevent excessive GWG.	Primary maternal outcome: GWG. Secondary outcomes: changes in diet and physical activity and incidence of macrosomia.	N=105 all BMI categories I: n=49 n=8 (17%) BMI ≥ 26 kg/m^2 C: n=56 n=2 (4%) BMI ≥ 26 kg/m^2 No published ethnicity data	I: Diet and physical activity. Individual counseling on PA and diet at 5 routine visits to a maternity health care nurse from 8-9 to 37 weeks gestation Option to attend supervised group PA sessions 1x/week until 37 weeks gestation. Dietary advice included: regular meals, consumption of fruit, vegetables and high fibre bread, restricting sugary snacks. C: Standard antenatal care.

Ronnberg et al. (2014)	*Sweden* RCT	To evaluate if a feasible, low-cost intervention could decrease the percentage of women gaining weight above the IOM recommendations on GWG.	Primary outcome: GWG.	N= 374 all BMI categories I: n = 192 BMI: 25.2 ± 4.9 kg/m^2 C: n= 182 BMI: 25.3 ± 4.8 kg/m^2	I: Physical activity only. Individual education about IOM guidelines for recommended GWG according to BMI category at first antenatal visit. Personalised graphs including recommended interval of GWG were provided. Recommendation of PA during pregnancy; a moderate level of exertion during a total of approximately 30 mins/day. Activities should entail a minimal risk of falling fetal injury. Activities were based on personal interests and abilities. Activities could also be adjusted during pregnancy. C: Standard antenatal care.
Luoto et al. (2011) NELLI study	*Finland* Cluster-RCT	To determine if lifestyle counselling in pregnant women at high risk of GDM can prevent GDM or macrosomia.	Primary maternal outcome: GDM. Primary infant outcome: birthweight. Secondary outcomes: GWG, insulin treatment during pregnancy.	N=399 all BMI categories I: n=219 BMI: 17.0-48.5 kg/m^2 C: n=180 BMI: 17.2-37.8 kg/m^2 No published ethnicity data	I: Diet and physical activity. Intervention from 8-12 weeks to 37 weeks gestation. Recommendations provided for GWG. PA sessions (from 8-12 weeks gestation) and dietary counselling sessions (from 16-18 weeks) were offered The aims of the sessions were to increase leisure time PA and to adhere to Finnish dietary recommendations regarding the proportions of fats, sugar, fibre, fruit and vegetables. Further PA and dietary counselling subsequently provided at each antenatal visit. C: Standard antenatal care.
Obese only (BMI ≥30 kg/m^2)					
Poston et al. (2015) UPBEAT study	*UK* RCT	To determine if a dietary and physical intervention could reduce incidence of GDM and macrosomia.	Primary maternal outcome: GDM. Primary infant outcome: macrosomia. Secondary outcomes: dietary measures, physical activity scores, GWG, maternal anthropometric	N = 1555, obese women I: n=783, 36.3 ± 5.0 kg/m^2 C: n=772, 36.3 ± 4.6 kg/m^2 Ethnicity, n (%) White I: 483 (63) C: 490 (63) Black I: 200 (26) C: 202 (26) Asian I: 48 (6) C: 47 (6) Other I: 41 (5) C: 44 (6)	I: Diet and physical activity. Eight health trainer-led group/individual sessions of 1h duration 1x/week over 8 weeks starting between 15-18 weeks gestation - Material covered over phone/email if participant could not personally attend session. Women received advice on strategies used to achieve goals, behavioural change, provided with booklets with recommended foods, recipes and suggestions for physical activity (DVDs of an exercise regimen that was safe for pregnancy, a pedometer, and a log book for recording their weekly goals).

			measurements and blood biochemistry.		The aim was to promote a healthy pattern of eating but not necessarily to restrict energy intake, and tailored to the woman's habitual diet and cultural preference. Exchanging carbohydrate-rich foods with a medium-to-high GI for those with a lower GI to reduce the GL was suggested, as was restricting dietary intake of SFA. incremental increases in walking from a pedometer assessed baseline were advised. C: Standard antenatal care.
Vesco et al. (2014) Health Moms Trial	*USA* RCT	To determine if a weight management intervention can limit GWG in obese pregnant women.	Primary maternal outcome: GWG. Secondary outcomes: weight change at 1 year postpartum, proportion of infants with birth weight>90th percentile for gestational age.	N = 114 obese women I: n=56, 36.7 ± 5.2 kg/m^2 C: n=58, 36.8 ± 4.7 kg/m^2 Ethnicity, n (%) White I: 49(88) C: 49(85)	I: Diet and physical activity. Two weekly individual dietary counselling sessions provided <21 weeks' gestation. Participants attended weekly group meetings until delivery. Daily food and activity diaries were recommended and reviewed weekly. Each group session included: check-in, a nutrition and/or exercise topic, a behaviour change topic, a goal-setting segment for the following week and a plan for how to meet goals. The goals were: to maintain weight within 3% of the original weight (at randomisation), to keep calorie intake within the individual goal, to adopt a sodium-restricting diet and to exercise daily (30 min moderate daily activity/10000 pedometer steps daily). C: Standard antenatal care.
Vinter et al. (2011) LiP Study	*Denmark* RCT	To study the effects of lifestyle intervention on GWG and obstetric outcomes.	Primary maternal outcomes: GWG, incidence of preeclampsia, pregnancy-induced hypertension, GDM, caesarean section. Primary infant outcomes: macrosomia and NICU admissions.	N = 304 obese women I: n=150, 33.4 kg/m^2 (31.7 – 36.5) C: n=154, 33.3 kg/m^2 (31.7 – 36.9) No published ethnicity data	I: Diet and physical activity. Recruitment from 10-14 weeks. Four individual dietary counselling sessions with trained dietitians to provide a personalised diet. Encouragement to be moderately physically active for 30-60 minutes daily. Free, full-time memberships to a fitness centre. C: Standard antenatal care.

Abbreviations: BMI, body mass index; C, control; GDM, gestational diabetes mellitus; GI, glycaemic index; GL, glycaemic load; GWG, gestational weight gain; I, intervention; LiP, lifestyle in pregnancy; NICU, neonatal intensive care unit; PA, physical activity; RCT, randomised controlled trial; UPBEAT, UK pregnancy better eating and activity trial.

3.4.4 Antenatal intervention

Gestational age at commencement of the antenatal lifestyle intervention ranged from 7 to 21 weeks' gestation. Duration of the intervention varied widely; one RCT involved only a single point of contact for delivery of the intervention (Ronnberg et al., 2015). The most intensive intervention involved participants attending an average of 20±7 (range 0-28) weekly sessions (Vesco et al., 2014). For the seven trials which included a dietary component interventions aimed to reduce glycaemic index (GI) (Walsh et al., 2012; Poston et al., 2015) reinforce existing standard healthy eating guidelines (Kinnunen et al., 2007; Luoto et al., 2011) provide dietary consultations with dietitians to develop personalised diet plans based on standard healthy eating guidelines (Vinter et al., 2011; Vesco et al., 2014) or reduce intake of energy-dense and high-fat foods in order to decrease excessive GWG (Rauh et al., 2013) For the seven trials which included physical activity, the intervention included free fitness club membership (Vinter et al., 2011) verbal encouragement for daily exercises (Walsh et al., 2012; Rauh et al., 2013), trainer-led physical activity sessions (Kinnunen et al., 2007; Luoto et al., 2011), formalised prescription of exercise and regular monitoring of GWG at every anatenatal visit (Ronnberg et al., 2015) and provision of DVD exercise regimens, a pedometer and logbook, and recommended goals for incremental increases in walking (Poston et al., 2015).

3.4.5 Antenatal controls

Control groups received antenatal care standard for the study setting. This included formal dietary and GWG advice (Walsh et al., 2012) or routine healthy lifestyle advice for the respective country (Kinnunen et al., 2007; Luoto et al., 2011; Poston et al., 2015; Rauh et al., 2013; Ronnberg et al., 2015). One control group was informed about the purpose of study and of a website with healthy lifestyle advice (Vinter et al., 2011) while another received a single dietary advice session immediately after randomisation; this session was routinely covered by the insurance policy of the participating hospital (Vesco et al., 2014).

3.4.6 Outcomes of the antenatal interventions

The maternal and infant outcomes of the intervention are summarised in Table 3:5. GWG was a primary outcome of five trials (Kinnunen et al., 2007; Vinter et al., 2011; Rauh et al., 2013; Vesco et al., 2014; Ronnberg et al., 2015); all, apart from one (Kinnunen et al., 2007) reported a significant reduction in GWG the intervention arm. The remaining three trials included GWG as a secondary outcome (Luoto et al., 2011; Walsh et al., 2012; Poston et al.,

2015), of which two reported a significant reduction in GWG (Walsh et al., 2012; Poston et al., 2015). Three trials included GDM incidence as a primary maternal outcome (Luoto et al., 2011; Vinter et al., 2011; Poston et al., 2015), however none of these reported statistical differences in this outcome between the control and intervention arm. Birth weight, incidence of LGA infants and macrosomia were the primary outcome of four maternal RCTs (Luoto et al., 2011; Vinter et al., 2011; Walsh et al., 2012; Poston et al., 2015), with only one trial showing a significant result (Luoto et al., 2011). Two trials included macrosomic newborns and incidence of LGA as secondary outcomes, both of which were significantly lower in the intervention arm (Kinnunen et al., 2007; Vesco et al., 2014).

3.4.7 Study quality

The overall quality of the included offspring follow-up studies varied and is summarised in Table 3:6; two studies were classified as moderate risk (Kolu et al., 2016; Vesco et al., 2016), one as high (Mustila et al., 2012) and the remaining five studies as low risk (Tanvig et al., 2014; Rauh et al., 2015; Horan et al., 2016; Patel et al., 2017a; Ronnberg et al., 2017). The main source of bias across all studies was the high rate of participant attrition to offspring follow-up. For the antenatal interventions all of the trials were classified as low risk (Luoto et al., 2011; Vinter et al., 2011; Walsh et al., 2012; Rauh et al., 2013; Vesco et al., 2014; Poston et al., 2015; Ronnberg et al., 2015), except for one trial which was classified as moderate risk (Kinnunen et al., 2007).

Table 3:5 : Impact of antenatal lifestyle intervention on primary and secondary outcomes of the antenatal RCT

Publication	Primary outcomes	Secondary/additional outcomes
All BMI categories		
Walsh et al. (2012)	Infant outcome: No effect on birthweight.	Less GWG in women in the intervention arm (12.2 vs 13.7 kg, p=0.01). Glucose intolerance significantly lower in intervention arm, 21% vs 28% (p=0.02).
Rauh et al. (2013)	Maternal outcome: lower proportion of women exceeding GWG with IOM guidelines from the intervention group (38% vs 60%) (OR: 0.5; 95% CI: 0.3 to 0.9).	Participants in the intervention group gained less weight than those in the control group (-1.7; 95% CI: -3.0 to -0.3; p=0.035), only 17% of women in the intervention showed substantial weight retention (more than 5 kg) at 4-month pp compared to 31% in the control arm. No significant difference in obstetric outcomes.
Kinnunen et al. (2007)	Maternal outcome: No effect on GWG.	Healthier diets maintained in I versus C during pregnancy. There were no macrosomic babies in the intervention group, but eight (15%) in the control group (p=0.006).
Ronnberg et al. (2014)	Maternal outcome: No effect on the proportion of women exceeding the IOM guidelines for GWG (41.1% vs 50.0%, p=0.086).	Difference in mean GWG I: 14.19kg (4.45 SD) C: 15.31kg (5.38 SD).
Luoto et al. (2011)	Maternal outcome: No effect on GDM. Infant outcome: birthweight lower in the intervention than usual care group (3,532±514g *vs* 3,659±455g, p=0.008).	Total GWG, preeclampsia, or use of diabetic medication did not differ between the groups. Women in the intervention group increased intake of fibre (AC 1.83, 95% CI 0.30–3.25, p=0.023) and PUFAs (AC 0.37, 95% CI 0.16–0.57, p=0.001), decreased intake of SFA (AC−0.63, 95% CI −1.12 to −0.15, p=0.01) and intake of saccharose (AC −0.83, 95% CI −1.55 to −0.11, p=0.023), than women in the usual care group.
Obese only (BMI ≥30 kg/m^2)		
Poston et al. (2015)	Maternal outcome: No effect on GDM. Infant outcome: No effect on macrosomia.	Maternal dietary quality, assessed by total energy intake, GI and macronutrient intake all lower in intervention group (p<0.002). PA (p<0.002), GWG (p=0.041) and adiposity, defined as sum of skinfold (p<0.002), were reduced in the intervention group.
Vesco et al. (2014)	Maternal outcome: Between baseline and 34 weeks gestation, intervention participants gained less weight (5.0 vs. 8.4 kg; p<0.001).	Reduced prevalence of LGA in the intervention group compared to the control group (9% vs 26% p=0.02).
Vinter et al. (2011)	Maternal outcomes: Reduction in GWG with intervention compared to control (7.0 vs 8.6 kg; p=0.01). Infant outcome: No significant effect on macrosomia and NICU admissions.	No effect for other obstetric outcomes.

Abbreviations: AC, adjusted coefficient; C, control; GDM, gestational diabetes mellitus; GI, glycaemic index; GWG, gestational weight gain; I, intervention; IOM, Institute of Medicine; LGA, large for gestational age; OR, odds ratio; PA, physical activity; pp, post-partum; PUFAs, polyunsaturated fatty acids; RCT, randomised controlled trial; SFA, saturated fatty acids.

Table 3:6: Sources of bias in offspring follow-ups following antenatal lifestyle interventions in publication order of offspring follow-up

Author	Study design	Randomisation	Allocation	Attrition	Risk of bias
Follow-up					
Mustila et al. (2012)	Quasi-RCT	HIGH	UNCLEAR	HIGH	HIGH
Rauh et al. (2015)	Cluster-RCT	LOW	LOW	LOW	LOW
Tanvig et al. (2015)	RCT	LOW	LOW	HIGH	LOW
Horan et al. (2016)	RCT	LOW	LOW	HIGH	LOW
Kolu et al. (2016)	Cluster-RCT	LOW	UNCLEAR	HIGH	MODERATE
Vesco et al. (2016)	RCT	LOW	UNCLEAR	HIGH	MODERATE
Patel et al. (2017)	RCT	LOW	LOW	HIGH	LOW
Ronnberg et al. (2017)	RCT	LOW	LOW	LOW	LOW
Antenatal					
Kinnunen et al. (2007)	Quasi-RCT	HIGH	UNCLEAR	LOW	MODERATE
Rauh et al. (2013)	Cluster-RCT	LOW	LOW	LOW	LOW
Vinter et al. (2011)	RCT	LOW	LOW	LOW	LOW
Walsh et al. (2012)	RCT	LOW	LOW	LOW	LOW
Luoto et al. (2011)	Cluster-RCT	LOW	UNCLEAR	LOW	LOW
Vesco et al. (2014)	RCT	LOW	UNCLEAR	LOW	LOW
Poston et al. (2015)	RCT	LOW	LOW	LOW	LOW
Ronnberg et al. (2014)	RCT	LOW	LOW	LOW	LOW

Abbreviations: RCT, randomised controlled trial

3.5 Discussion

The findings of this systematic review, focusing on the impact of antenatal interventions on offspring adiposity, highlight considerable heterogeneity in the methodological design and reported outcomes in the included publications. In two of the publications (n=787) focusing on obese women only, the authors reported reduced measures of adiposity defined as subscapular skinfold thickness and weight-for-age z-score, at 6 and 12 months, respectively. However, the remaining six studies found no effect on measures of adiposity in their offspring. These studies included offspring from 6 months to 7 years. Five trials included women from all BMI categories, and one trial included obese women only.

3.5.1 Antenatal interventions

Considerable variation was found in the study design, recruitment and intensity of the antenatal interventions. For the eight trials identified gestational age at recruitment ranged from 7 to 21 weeks. This variability existed both between (Kinnunen et al., 2007; Walsh et al., 2012) and within the studies (Vesco et al., 2014). Most studies recruited between the end of the first trimester/middle of second trimester. It is plausible that earlier, and thus longer, interventions could have a more pronounced effect on offspring obesity, especially if the intervention commenced prior to conception (Poston et al., 2016). This is suggested by an observational study of siblings born to obese mothers pre- and post-bariatric surgery, in which childhood adiposity was lower in the sibling born after bariatric surgery (Smith et al., 2009). Given that there are potential limitations in initiating interventions in early pregnancy preconception weight loss could be an important strategy in overweight and obese women, although this is may be difficult to achieve due to the high incidence of unplanned pregnancies in developed countries; 45.2% in the UK (Wellings et al., 2013) and 49.0% in the USA (Finer and Zolna, 2011).

Considerable variation was also found in the intensity of the interventions; which mirrors previous reviews (Dodd et al., 2010; Oteng-Ntim et al., 2012; Thangaratinam et al., 2012; Flynn et al., 2016a). The number of intervention sessions offered to the mothers varied between 1 to 28. Of the two trials which showed a reduction in infant adiposity Vesco et al. offered weekly group meetings following two individual meetings, each of these sessions lasting up to 90 minutes and on average participants attended 20±7 sessions (Vesco et al., 2014). Poston et al. also showed a reduction in infant adiposity and this was the only study to reach out to mothers who could not attend the prescribed meetings in person, by email

or telephone (Poston et al., 2015). This may have contributed to efficacy of the intervention, as a systematic review of technology use in antenatal lifestyle intervention trials has highlighted the benefits of harnessing technology as a tool of delivering the intervention (O'Brien et al., 2014). Adherence to the original study protocol was discussed in three trials; the UPBEAT trial reporting that women completed on average 7 of the 8 sessions provided (Poston et al., 2015) and two other trials, ROLO and the Healthy Moms Trial reported 75% (Walsh et al., 2012) and 80% (Vesco et al., 2014) adherence respectively to the intervention. As mentioned, the follow-up publications (Vesco et al., 2016; Patel et al., 2017a) of the UPBEAT (Poston et al., 2015) and Health Moms (Vesco et al., 2014) trials found a significant reduction in measures of adiposity in the offspring at ages 6 and 12 months respectively, suggesting that adherence to the antenatal protocol is a likely determinant of effects on infant adiposity.

3.5.2 Offspring measures of childhood adiposity

There was significant heterogeneity in the types of offspring measures of adiposity undertaken. There is no ideal measurement of infant or childhood adiposity, and a balance between costs, efficiency, age of the child and ease of collection influences the type of data collected. BMI z-scores or BMI were analysed by five studies and adjusted for infant age and gender and reported as standard deviations (SD) from the mean (Tanvig et al., 2014; Horan et al., 2016; Kolu et al., 2016; Patel et al., 2017a; Ronnberg et al., 2017). However, BMI is an inaccurate estimate of body fat mass in children, and the same thresholds do not apply as in the adult population. To gain an accurate understanding of body composition in infants and children, other methods such as infant-sized air-displacement plethysmography (PEAPOD), skinfold thicknesses, DXA and bioelectric impedance analysis (BIA) are more appropriate. PEAPOD and DXA are considered to be the gold standard for measuring body composition for infants and children, respectively. They provide reliable and accurate results for body composition; however, they are expensive, requires a trained technician and are time consuming.

Four studies collected skinfold thicknesses or body circumference data (Tanvig et al., 2014; Horan et al., 2016; Vesco et al., 2016; Patel et al., 2017a). Both are relatively simple and inexpensive measurements, useful for community paediatrics or large-scale studies, and provide information about body fat distribution if measured at various fat depots. However, training is necessary to obtain standardised measurements and they can be poorly

reproducible with increasing BMI values in children (Speiser et al., 2005). Subscapular skinfold thickness is recognised as an accurate predictor of central adiposity and it thought to have low measurement error (Mensink et al., 2003). This method was measured in three offspring follow-ups studies (Horan et al., 2016; Vesco et al., 2016; Patel et al., 2017a). Patel et al. observed a significant reduction in the intervention arm of the UPBEAT study in both the subscapular thickness z-score and absolute value. The authors conducted a causal mediation analysis which suggested that the change in subscapular skinfold thickness was due to improvements in the antenatal diet and a reduction in GWG (and not postnatal diet). Subscapular skinfold measurements are known to track into obesity in later life and have been associated with adverse metabolic outcomes in adulthood, including impaired glucose metabolism and increased serum cholesterol (Srinivasan et al., 2003; Santos et al., 2016). It therefore should be considered as a standardised, low cost, reliable method for use in future studies. Tanvig et al. performed DXA scans on the offspring. DXA scans offer an accurate measure of total body fat and serve as the gold standard for validation of other measures of obesity, however children are required to lie still for 5 minutes and therefore scanning children under the age of 4 years is a challenge (Jensen et al., 2015). Acceptability of a DXA scan by parents, the need to undertake the scan in a hospital setting, and the cost may outway the benefits for this measurement of body composition.

High rates of attrition were observed for six of the follow-up trials. Loss of participants to offspring follow-up may have been affected by the strategy for participant contact. Of the two offspring follow-up studies with the lowest attrition rates, in one, parents were emailed/phoned/mailed to obtain parent-measured data (Mustila et al., 2012). Measurement by untrained parents in this study and not healthcare professionals may have decreased the accuracy and quality of the data, compromising the validity. The second study relied on routinely collected paediatric clinical data, which carries a risk of bias due to the lack of standardised data collection techniques, but with the benefit of lower attrition (Rauh et al., 2015).

3.5.3 Offspring adiposity

Amongst the five RCTs that included women from all BMI categories, none found an effect of the intervention on measures of childhood adiposity. However, of the three studies which followed children of women with a BMI ≥30 kg/m^2, two found that up to 12 months of age, lifestyle interventions influenced infant body composition (Vesco et al., 2016; Patel et al.,

2017a). Other than an influence of greater adherence to intervention in the UPBEAT trial, this could also suggest a potentially greater influence of the intervention in obese women to improve lifestyle. Alternatively, effects in offspring of obese women might diminish over time, as Vinter et al. (2011) investigated children at 2.5-3.2 years of age and found no significant effects although younger children were not studied. Due to the heterogeneity of the interventions in obese women, the most beneficial intervention design cannot accurately be defined, and accords with the conclusion of Gardner et al. in an earlier review of lifestyle interventions in pregnancy and pregnancy outcomes (Gardner et al., 2011).

3.5.4 Potential biases in the review process

This systematic review has several strengths, including a comprehensive search strategy and compliance with guidelines from the Centre of Reviews Dissemination Systematic Review Guide and the PRISMA statement and checklist. For each offspring follow-up, full-text copies of the corresponding maternal publication were consulted. The review was limited by variability of the studies included, which limited the ability to perform meta-analyses. The possibility of publication bias should be considered because those studies not published in the English language were not included in this systematic review. During the selection of studies for this review, the authors of three antenatal intervention trials which had planned to complete offspring follow-up but had not yet published their results were contacted. Of those who replied, Renault et al. and Bogaerts et al. have recruited exclusively obese women and intend to report childhood outcomes. Results from these studies may enable a more substantive conclusion on the effect of antenatal interventions in offspring of obese women.

High attrition is common in long-term follow-ups of RCTs, and is influenced by multiple factors, including population demography, age at follow-up, nature of methods of outcome measurements and perceived benefit to participants (Fewtrell et al., 2008). For this review, the low number of offspring follow-up data may have diminished the strength of the evidence base. One potential solution to account for missing data is to complete an intention-to-treat (ITT) analysis. ITT analysis includes every subject who is randomised according to randomised treatment assignment. Only three of the included trials utilised this statistical method (Vesco et al., 2014; Poston et al., 2015; Ronnberg et al., 2015). The variation in standard care antenatal practices between the settings and countries of the included studies, could also have influenced the results.

3.5.5 Recommendations for future research and practice

This systematic review included studies with women from all BMI categories. Antenatal interventions were effective at reducing childhood adiposity in obese women only suggesting that analyses of offspring outcomes should potentially be analysed separately for BMI category, although for the smaller studies this would result in limited power. A further limitation was the variability of studies included: the heterogeneity of the antenatal interventions (duration, initiation and components of the intervention) and the variations in offspring methods used to define adiposity was such that a meta-analysis could not be performed. Additionally, ethnicity can impact the development of childhood obesity, and only two trials (Vesco et al., 2014; Poston et al., 2015) included ethnicity data for their participants, one of which stated that it was completed in multi-ethnic populations (Poston et al., 2015).

Future studies should consider standardising the methodological design to that which has been shown to date to be most effective. From this systematic review this would appear to be those in which dietary advice and physical activity was delivered most frequently with high adherence rates. Standardisation of the method of measurement of adiposity in children, which will depend to some extent on the age of the child, should also be considered. This could consist of repeated anthropometric measurements, of height, weight and circumferences, which can be plotted against relevant growth reference charts, therefore growth trajectories and any deviation or crossing of centiles could be observed throughout childhood. These precautions would reduce variability and enable meta-analyses which can contribute to the evidence-based public health guidelines. During the final preparation of this review a protocol was published by the International Weight in Pregnancy Collaboration. The authors, Dodd et al. aim to complete an individual participant data meta-analysis to evaluate the effects of lifestyle interventions in overweight and obese pregnant women, on both maternal outcomes and childhood adiposity at 3-5 years of age (Dodd et al., 2017). This analysis will be a welcome addition to the field. Furthermore, a recent systematic review investigating interventions during the first 1,000 days, from conception to two years of age, to prevent childhood obesity reported that individual or family based approaches via the clinical, community and home setting exert a positive effect on child growth (Blake-Lamb et al., 2016). Future studies, including antenatal interventions should consider such approaches to facilitate improve intervention engagement, retention and standardised approaches to follow-up in the post-natal period. These approaches, combined with system levels

interventions, may offer a supportive environment to foster sustained behaviour change to improve obesity risk in childhood and, potentially, through the life-course.

3.5.6 Conclusion

A large body of observational evidence proposes an association between the *in utero* nutritional environment and offspring obesity, although some studies show no association. RCTs have the potential to determine causality. This systematic review highlights the need for appropriately powered, well designed, follow-up trials of antenatal lifestyle interventions in pregnant women, specifically in those with obesity, amongst whom the interventions may have the most significant influence on childhood adiposity. The absence of RCTs with comparable methodological design and low attrition rates limit the ability to recommend a specific lifestyle change for gestational prevention of offspring obesity.

Chapter 4 : Adiposity and cardiovascular outcomes in 3-year-old children of participants in UPBEAT, a complex intervention in pregnant women with obesity.

4.1 Abstract

Introduction: Maternal obesity is associated with greater offspring adiposity and cardiovascular risk. UPBEAT was a randomised controlled trial of an intensive diet and physical activity intervention in 1,555 pregnant women with obesity; intervention led to a healthier maternal metabolic profile, improved diet and lower weight gain in pregnancy and reduced infant adiposity at 6-months.

Objective: To determine whether the UPBEAT intervention led to improved childhood adiposity and cardiovascular function and resulted in sustained improvements in maternal lifestyle behaviours 3 years after delivery.

Methods: We assessed childhood adiposity (body mass index, skinfolds thicknesses, body fat percentage, waist and arm circumferences), and cardiovascular function (blood pressure, resting pulse rate) and maternal diet, physical activity and anthropometry in UPBEAT mother-child dyads who attended a 3-year follow-up.

Results: 514 children were assessed at age 3-years (49% intervention, 51% standard antenatal care) representing 33% of the eligible sample. There was no difference in the primary outcome, subscapular skinfold thickness, between the intervention and control arms (mean difference -0.30mm (95%CI: -0.92, 0.31)). Other measures of adiposity demonstrated mean differences close to zero, except for the sum of skinfolds (-2.00mm; 95%CI: -4.64, 0.62). Intervention children had a non-significant lower odds overweight or obesity (OR 0.73; 0.50, 1.08). Resting pulse rate was lower in children of mothers randomised to the intervention (-5 beats/minute: -8.41, -1.07). Maternal dietary improvements observed in the UPBEAT trial, including saturated fat and energy intake were maintained three years after delivery.

Conclusion: We found little evidence to support an effect of the intervention on child adiposity or cardiovascular outcomes at age 3-years, except for a reduction of resting pulse rate. Whilst this cohort is larger than previous studies there is potential for bias by loss to follow-up. The interesting observation of lower pulse rate in the intervention arm requires replication.

4.2 Introduction

The World Health Organisation (WHO) estimates that the global prevalence of childhood overweight and obesity will reach 70 million by 2025 (World Health Organisation, 2016). The causal pathways, widely explored in observational studies (Yu et al., 2013; Godfrey et al., 2017) suggest that maternal obesity may contribute to the development of childhood obesity through exposures during *in utero* development (Eriksson et al., 2014; Gaillard et al., 2015), which remain following adjustment for confounders (Dalrymple et al., 2019a; Heslehurst et al., 2019). These relationships have also been confirmed in animal studies, in which environmental and genetic contributions can be discounted (Patel et al., 2015). In contrast, observational studies using Mendelian randomisation, in which maternal genetic variants are used as instrumental variables to test the effect of maternal obesity on offspring adiposity do not support a causal intrauterine effect of greater maternal BMI on offspring adiposity (Lawlor et al., 2011; Fleten et al., 2012; Richmond et al., 2017). However, the majority of these studies are from populations of heterogenous BMI, and sibship analyses provide some evidence for an effect of high levels of maternal obesity on offspring adiposity (Smith et al., 2009).

Mother-child cohorts have reported associations between maternal obesity and cardiovascular morbidity and mortality rates in their children (Drake and Reynolds, 2010; Reynolds et al., 2013; Gaillard et al., 2014a) As reported by ourselves (Samuelsson et al., 2008, 2013) and others (Menting et al., 2019), the inference of *in utero* effects of maternal obesity on offspring cardiovascular function is also strongly supported by animal models; these describe a relationship between maternal obesity in experimental animals and offspring heart rate variability, cardiovascular response to stress, hypertension and higher circulating atherogenic lipids (Samuelsson et al., 2010; Penfold and Ozanne, 2015; Roberts et al., 2015), observations which have consistently been reported across species.

Many antenatal randomised controlled trials have reported diet and/or physical activity interventions in pregnant women with the primary aim of reducing gestational weight gain (GWG) or improving pregnancy outcomes (Flynn et al., 2016a). Whilst clinical outcomes have not overall been improved, the majority of interventions have shown some benefit in limiting GWG and improving diet (i-WIP Collaborative Group, 2017). Through follow up of the children, these RCTs provide an important opportunity to address the causal relationship between maternal obesity and subsequent obesity and cardiovascular risk in the child.

However, few studies have continued to childhood assessment and if performed the sample size has been inadequate to detect a meaningful effect size (Dalrymple et al., 2018b).

The UK Pregnancies Better Eating and Activity Trial (UPBEAT), was a multi-centre RCT of a dietary and physical activity intervention in 1,555 pregnant women with obesity (Poston et al., 2015). Women were randomised to an intense 8-week behavioural intervention or to standard antenatal care. The intervention had no effect on the primary outcomes, incidence of gestational diabetes and large for gestational age (LGA) infants. However, there were improvements in several secondary maternal outcomes; specifically, a reduction in total GWG and lower sum of skinfold thicknesses, an improvement in maternal antenatal glycaemic load (GL) and saturated fat intake (SFA) and a modest increase in self-reported physical activity. The intervention also contributed to a healthier metabolic profile across pregnancy (Mills et al., 2019). At 6-months postpartum we found the maternal dietary benefits of the intervention were sustained and that the intervention resulted in lower infant subscapular skinfold thicknesses (Patel et al., 2017a). The aim of the present study was to assess whether the UPBEAT intervention led to improved childhood adiposity and cardiovascular function and sustained improvements in maternal lifestyle behaviours 3 years after delivery.

4.3 Methods

4.3.1 Study design and setting

This study is a secondary analysis of the UPBEAT trial (Poston et al., 2015) We undertook a three-year follow-up from the UPBEAT study in the eight trial centres. In the original study, women with obesity (≥16 years of age; pre-pregnancy BMI≥30kg/m^2), were recruited in early pregnancy, exclusion criteria included pre-existing disease and multiple pregnancy. The participants were randomised to the intervention or standard antenatal care at 15^{+0}–18^{+6} weeks' gestation as reported previously (Briley et al., 2014). In brief, the intervention comprised dietary recommendation to reduce GL and SFA intake and to increase physical activity over an 8-week period. The intervention was delivered by health trainers.

4.3.2 Participants and consent

Consent to the trial included agreement to contact the participants at a later date (UK integrated research application system, reference 09/H0802/5). The follow-up study design and protocol were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 13/LO/1108). Between August 2014 and October 2017, all participants of the trial were invited to attend a 3-year post-delivery visit with their child (Poston et al., 2015). Research midwives/research assistants completed the data collection. Continued training and regular contact between the sites was sustained throughout the data collection period. Women were excluded from the analysis if they were pregnant or had given birth in the previous 4 months at the time of follow-up. Children were excluded if they were suffering from severe illness which could affect growth or development or if they were born before 34 weeks' gestation.

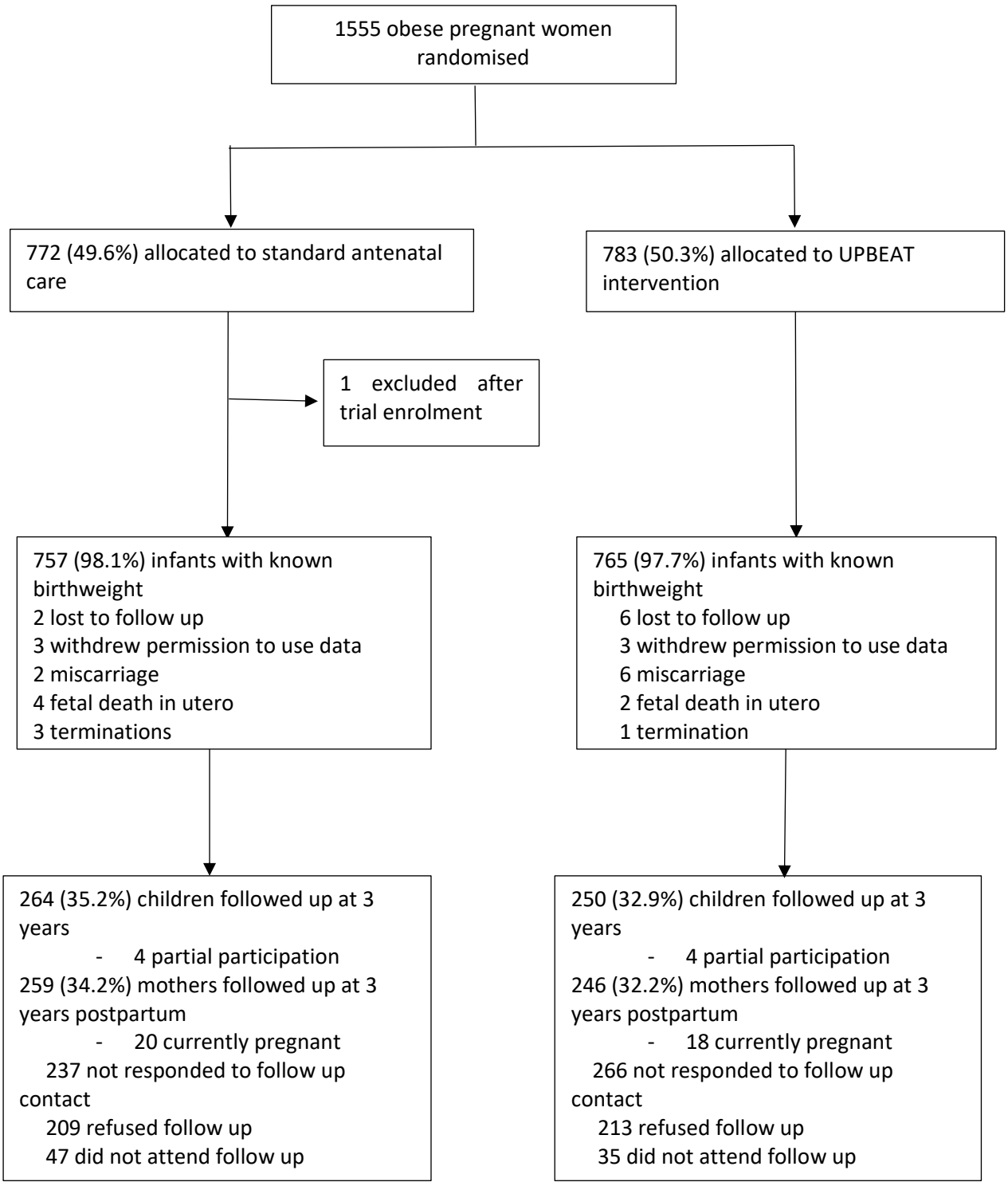


Figure 4:1: Consort diagram of participants enrolled in the UPBEAT trial at 3-years after delivery

4.3.3 Childhood outcomes

The principal offspring outcome (pre-specified) of interest was childhood adiposity assessed by subscapular skinfold thickness measured in triplicate using Holtain children skinfold callipers. Secondary offspring outcomes included triceps, biceps, suprailiac and abdomen skinfold thicknesses, sum of skinfold thickness (calculated by addition of the five measures), mid-upper arm and waist circumferences, estimated total body fat percentage assessed by bioelectrical impedance analysis (BIA, ImpediMed SFB7), weight (using a calibrated scale), WHO growth standard BMI z-score (de Onis, 2006) and age adjusted International Obesity Task Force (IOTF) BMI centiles. The WHO reference standards are adjusted for age and sex and are applicable irrespective of ethnicity and mode of early infant feeding. Childhood overweight and obesity were defined by IOTF sex-specific centiles (90.5th and 98.8th centiles for boys and 89.3th and 98.6th centiles for girls) (Cole and Lobstein, 2012).

For the BIA, the child was asked to lie on the couch for five minutes during data collection, after which blood pressure and resting pulse rate were recorded by a WelchAllyn 53S00-E4 device, with an appropriately sized arm cuff for the child. The measurements were completed in this order to ensure pulse rate was a resting value. Blood pressure was converted to age and height appropriate centiles (Flynn et al., 2017).

4.3.4 Maternal outcomes

At the 3-year visit maternal diet and physical activity were assessed using the same questionnaires as in the UPBEAT study (Briley et al., 2014). A semi-quantitative food frequency questionnaire was used to estimate dietary GL, macronutrient and energy intake. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) and summarised as metabolic equivalents (METs) of energy expenditure (The IPAQ Group, 2005). Maternal anthropometric measurements at the 3-year follow-up included mid upper arm, waist and thigh circumferences, subscapular, triceps, biceps, and suprailiac skinfold thicknesses (measured in triplicate using skinfold callipers) and BMI, calculated from weight and height data using the same standardised methods as the main UPBEAT study (Briley et al., 2014).

4.3.5 Statistical analyses

For summary statistics, binary and categorical variables are presented using counts and percentages. The distribution of continuous variables was assessed using coefficients of

skewness and then summarised by mean and standard deviation or median and interquartile range where appropriate. Comparison of demographic details was made between the intervention and control groups; if the outcome of interest was binary, an odds ratio was calculated, when categorical, chi-squared test was used. Mann-Whitney U tests or t-tests were used for continuous data, depending on the normality of the data.

4.3.6 Effect of intervention on maternal and offspring outcomes 3-years after delivery

To analyse the effect of the intervention, a complete case analysis was undertaken for all participating mothers and children. Treatment effects for continuous outcomes were expressed as differences in means obtained from multivariable linear or quantile regression. Linear regression was used for most outcomes, with quantile regression used for sum of skinfolds and maternal physical activity as the data was positively skewed. Binary endpoints were expressed as odds ratios with 95% confidence interval using logistic regression. Analyses were adjusted for minimisation variables (maternal BMI at trial enrolment, parity and ethnicity) and child sex and age at follow-up.

4.3.7 Sensitivity analyses to explore selection bias due to loss to follow-up

Although loss to follow-up was similar in each trial arm, we explored potential selection bias due to loss to follow-up by comparing the effect of the intervention versus standard care on maternal baseline characteristics and neonatal outcomes for those included in this analysis and those lost to follow-up.

For the offspring outcomes we used multivariate imputation chained equations to impute missing data for childhood adiposity and cardiovascular outcomes for the complete data set (n=1520). Data was imputed to create 50 datasets using 10 burn-in iterations for live-born infants using the following multivariate equation: maternal BMI (at baseline), age, ethnicity, parity, GDM diagnosis, centre of treatment, mode of feeding on hospital discharge. The multivariate imputation assumes missing at random (MAR) and can also increase statistical power and enables exploration of whether loss to follow-up resulted in type-2 statistical errors.

4.4 Results

4.4.1 Participants

Of the 1,555 participants randomised to the UPBEAT trial 1,233 were approached between 3-4 years after delivery and 1,017 responded to contact. Of these, 33% of those originally randomised, n=514 children and mothers took part (n= 250 intervention; 264 standard antenatal care), Figure 4:*1*. Of these 514 mother-child pairs, 506 had complete outcome data, with the remaining 8 contributing only to questionnaire data completed at home. Nine children were excluded on the basis of severe illness or delivery <34 weeks' gestation. For those who completed the follow-up there was no difference in the majority of maternal baseline (trial entry) characteristics Table 4:1 or neonatal characteristics (Table 4:2) between the intervention and standard care arm, except for a higher odds ratio of LGA for infants in the intervention arm. Also, mothers who attended the 3-year follow-up were on average, compared to those who did not attend, older (1.1 years), more likely to be Caucasian or nulliparous, and less likely to smoke (Table 4:4). There was a higher proportion of breastfeeding on hospital discharge for infants who completed the 3-year follow-up (Table 4:*5*). In this sub-population (n=514), and in common with the original trial, sum of maternal skinfold thicknesses at 26^{+0}-28^{+6} weeks' gestation were lower in the intervention arm compared to the standard care arm, as were GL and reported SFA intake (Table 4:6). In common with the main trial population physical activity was increased in those in the intervention arm (Table 4:4). In contrast to the main trial, there was no difference in total GWG between the intervention and control groups (7.3kg vs 7.6kg *p*=0.26 (Table 4:4). or the metabolic profile in pregnancy (Figure 4:*2*, Figure 4:*3*) (Poston et al., 2015; Mills et al., 2019).

4.4.2 Intervention effects on childhood adiposity outcomes

34% of all children with adiposity measurements were classified as overweight or obese, with 8% being obese. The mean (standard deviation) BMI z-score was 0.88 (1.0). There was no statistical evidence for a difference in measures of offspring adiposity between the intervention and standard care arms (Table 4:3: UPBEAT 3-year follow-up: Child anthropometry at 3-years of age, by randomisation arm). For the primary outcome of subscapular thickness the adjusted difference in mean (aMD) was -0.30mm, for sum of skinfold thicknesses (SSF) -2.00mm (95% CI -4.64 to 0.62) and for body fat percentage (by bioelectrical impedance analysis) (aMD) -0.30% (95% CI -1.62 to 1.01). There was a non-significant lower odds of being classified as overweight or obese in the intervention; 73 vs 93, (OR 0.73; 0.50, 1.08).

There were no differences in the adjusted coefficients for BMI z-score, waist circumference and mid-upper arm circumference between trial arms (Table 4:3).

4.4.3 Intervention effects on child cardiovascular outcomes

A trend towards lower diastolic blood pressure for children born to mothers from the intervention arm (-2.98; -7.76, 1.08) did not reach statistical significance (Table 4:3). Resting pulse rate was -5 (-8.41 to -1.07) beats per minute (bpm) lower in the intervention arm, compared with standard care (Table 4:3). Further analysis identified a bimodal distribution for pulse rate (Figure 4:*4*). This bimodality was not associated with maternal dietary intake and resting pulse rate in pregnancy, child dietary intake, physical activity, sedentary time and time of day, season or trial centre. Logistic regression identified a shift from the higher (76-135bpm) to the lower (45-75bpm) modality as a result of the intervention; odds ratio 0.54 (0.32, 0.90). Sensitivity analyses using multiple imputation for the whole trial population demonstrated this significant difference in resting pulse rate was sustained (range -8.7 to -0.98 bpm; Table 4:9).

4.4.4 Effect of the antenatal intervention on maternal diet and body composition 3 years after delivery

Compared to women who received standard care, women in the intervention arm who provided complete dietary data reported lower maternal energy and SFA intake and higher protein intake 3 years after delivery (Table 4:7).

Figure *4*:*5* shows this data with previous measurements taken throughout pregnancy and at 6 months postpartum for the trial population at each time point, showing a sustained effect of the intervention. Women were excluded if they under-reported calorie intake. There were no differences in self-reported physical activity or in measures of body composition (Table 4:7, Table 4:**8**).

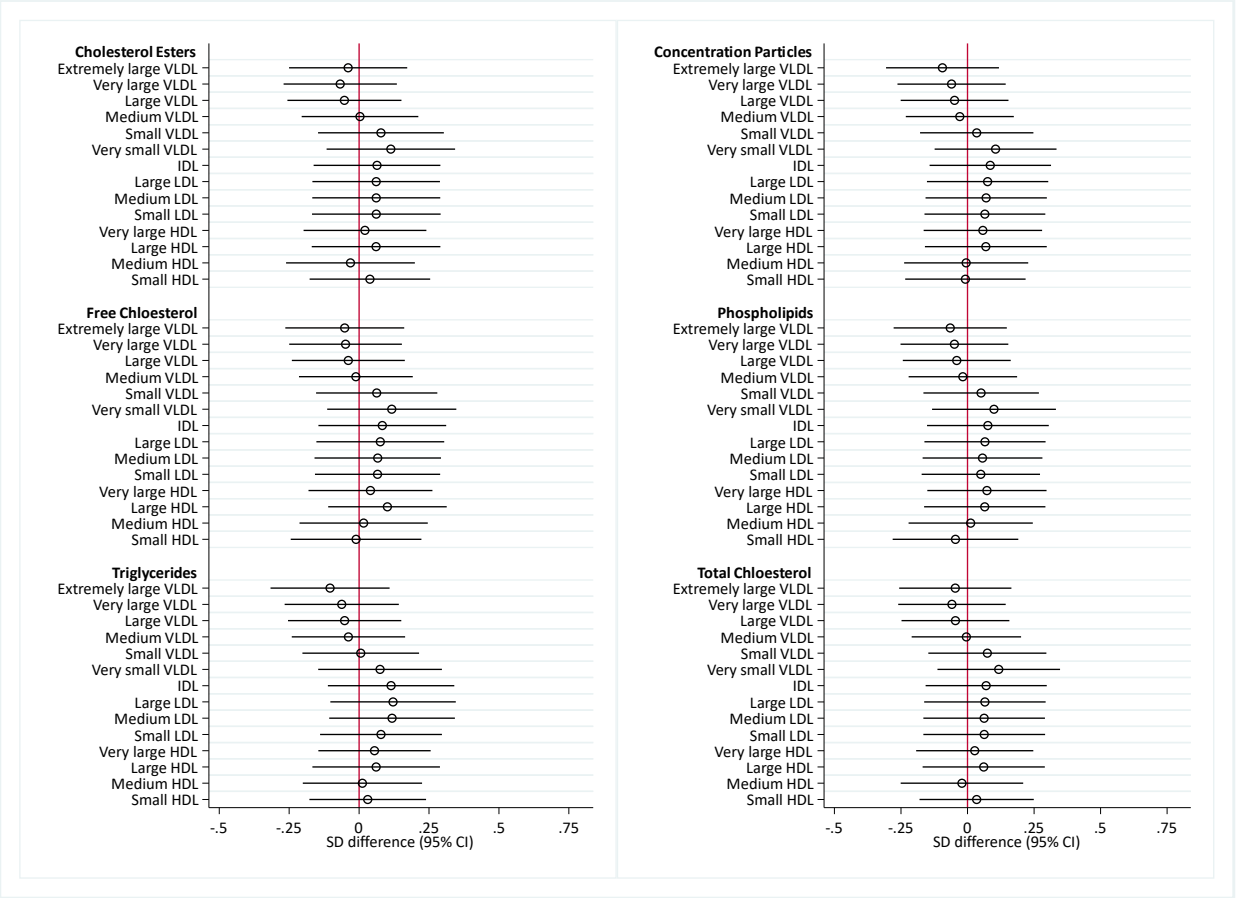


Figure 4:2: Metabolites part 1: Effect of the UPBEAT intervention (difference in mean rate of change for each metabolic measure in SD units per 4 weeks of gestational age comparing those in the intervention arm to those receiving standard care) on mean rate of change in metabolic traits in SD units per 4 weeks for the women who attended the 3-year follow-up (n=322)

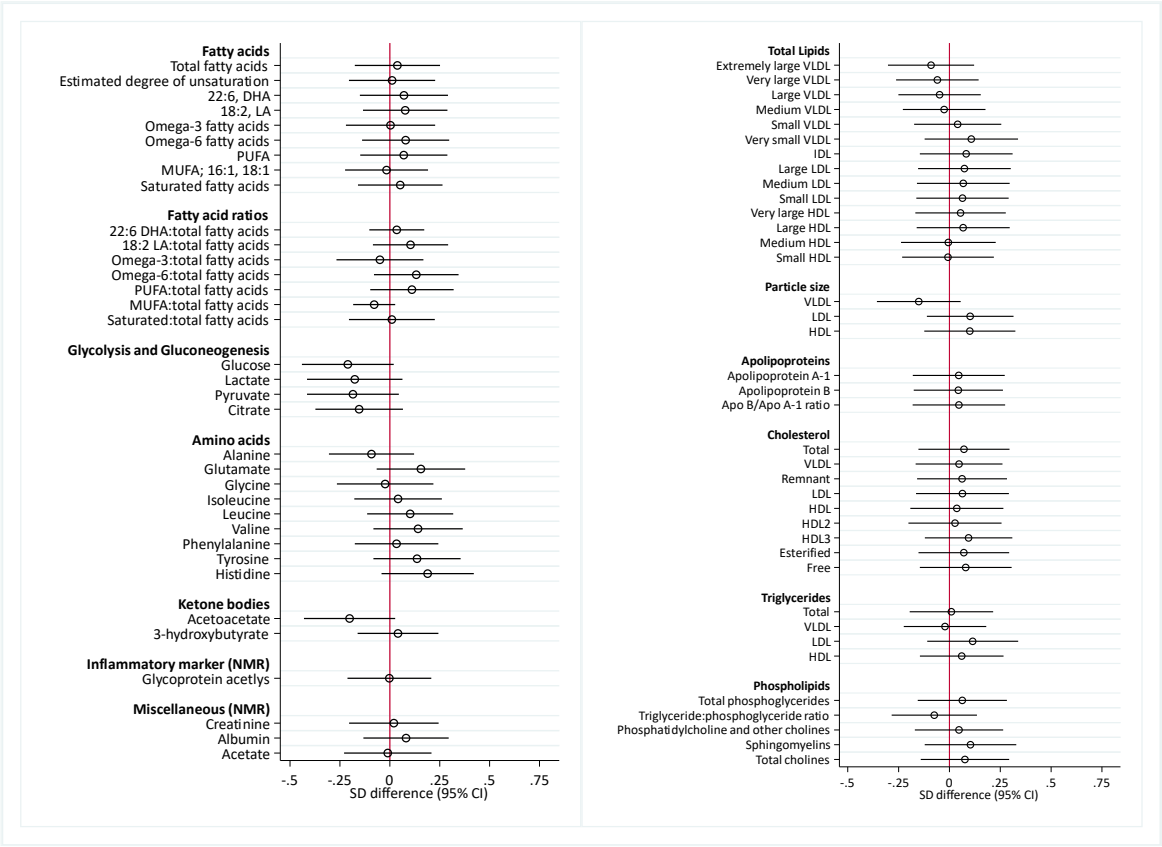


Figure 4:3: Metabolites part 2: Effect of the UPBEAT intervention (difference in mean rate of change for each metabolic measure in SD units per 4 weeks of gestational age comparing those in the intervention arm to those receiving standard care) on mean rate of change in metabolic traits in SD units per 4 weeks for the women who attended the 3-year follow-up (n=322)

Table 4:1: UPBEAT 3-year follow-up: Comparison of maternal characteristics of those who attended the 3-year follow-up, by randomisation arm.

Maternal		Intervention		Control		Mean difference/ OR (95%CI)
		Mean (SD)/ Median (IQR) N (%)				
Age (years) at baseline		250	31.2 (5.0)	264	31.3 (5.5)	-0.09 (-1.01 to 0.82)
BMI (kg/m^2) at baseline		250	34.5 (32.5-38.0)	264	34.9 (32.6-37.8)	-0.14 (-0.96 to 0.68)
ethnicity	Asian	250	13 (5)	264	9 (3)	1.47 (0.61 to 3.52)
	Black		55 (22)		64 (24)	0.87 (0.57 to 1.32)
	White		173 (69)		176 (67)	ref
	Other		9 (4)		15 (6)	0.61 (0.26 to 1.43)
Multiparous		250	124 (50)	264	138 (52)	0.90 (0.63 to 1.27)
Smoking status at baseline		250	5 (2)	264	14 (5)	0.88 (0.56 to 1.38)
IMD quintiles*	1 (least deprived)	247	14 (6)	264	16 (6)	0.78 (0.36 to 1.68)
	2		21 (8)		15 (6)	1.24 (0.61 to 2.55)
	3		28 (11)		30 (11)	0.83 (0.46 to 1.50)
	4		75 (31)		106 (40)	0.63 (0.42 to 0.94)
	5 (mot deprived)		109 (44)		97 (37)	ref
Sum of skinfolds (cm) at baseline		246	121.6 (29.5)	263	122.7 (25.7)	-1.15 (-5.97 to 3.66)
Antenatal characteristics	GDM**	234	56 (24)	250	69 (27)	0.82 (0.55 to 1.24)
	PE¥	249	6 (2)	260	10 (4)	0.62 (0.22 to 1.72)
	Total GWG from 15-18 weeks¶	222	7.3 (4.5)	230	7.7 (4.2)	-0.38 (-1.17 to 0.42)

*Abbreviations: BMI, body mass index; CI, confidence intervals; GDM, gestational diabetes; GWG, gestational weight gain; IMD, indices of multiple deprivation; IQR, interquartile range; PE, pre-eclampsia; SD, standard deviation. *IMD quintiles are calculated for the region of residence, by fifths of the population. UK wide scores were developed by reconciling Scottish data to English norms. ** Gestational diabetes (GDM) diagnosis by International Association of Diabetes in Pregnancy Study Group criteria at 27^{+0} to 28^{+6} weeks' gestation. ¥ Pre-eclampsia defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both, on at least two occasions 4 hours apart, with proteinuria ≥300 mg/ 24 hours. ¶Total gestational weight gain calculated using estimated weight before pregnancy and weight at 36 weeks'.*

Table 4:2 : UPBEAT 3-year follow-up: Comparison of neonatal characteristics of those who attended the 3-year follow-up, by randomisation arm.

		Intervention		Control		Mean difference/ OR (95% CI)
		Mean (SD)/ N (%)				
Birth characteristics	Gestation at birth (weeks)	250	39.8 (1.5)	264	39.5 (2.2)	0.25 (-0.07 to 0.58)
Anthropometry	Birthweight (grams)	250	3523 (526)	264	3426 (578)	97.2 (1.3 to 193.0)
	Birthweight >4kg	250	40 (16)	264	28 (11)	1.6 (0.95 to 2.69)
	LGA >90^{th†} Centile	250	39 (15)	264	25 (9)	1.76 (1.03 to 3.01)
	Subscapular skinfold thickness (mm)	113	5.7 (1.4)	113	5.5 (1.3)	0.24 (-0.13 to 0.61)
	Triceps skinfold thickness (mm)	115	5.3 (1.3)	119	5.2 (1.6)	0.08 (-0.30 to 0.47)
Neonatal feeding history at 72 hrs	Formula feeding	249	47 (19)	264	53 (20)	0.91 (0.58 to 1.43)
	Breast feeding		158 (63)		163 (62)	Ref
	Partially breastfeeding		44 (18)		48 (18)	0.94 (0.59 to 1.50)

Abbreviations: CI, confidence intervals; LGA, large for gestational age; OR, odds ratio; SD, standard deviation. † Customised birthweight centile adjusting for maternal height and weight, ethnicity, parity and sex of the infant.

Table 4:3: UPBEAT 3-year follow-up: Child anthropometry at 3-years of age, by randomisation arm.

	Intervention		Control		Mean difference/Odds ratio (95% CI)	p-value
	Mean (SD)/ Median (IQR) N (%)					
Child age at 3-year follow up (months)	250	41.8 (3.4)	264	41.8 (3.4)	0.05 (-0.53 to 0.64)	0.85
Weight (kg)*	240	17.2 (2.7)	254	17.1 (2.9)	0.16 (-0.30 to 0.63)	0.49
height (cm)*	241	101.1 (4.9)	252	100.8 (5.5)	0.34 (-0.46 to 1.14)	0.40
Subscapular skinfold thickness (mm)*	204	7.8 (3.2)	215	8.1 (3.4)	-0.30 (-0.92 to 0.31)	0.33
Triceps skinfold thickness (mm)*	216	12.3 (4.1)	228	12.1 (3.7)	0.23 (-0.49 to 0.97)	0.52
Biceps skinfold thickness (mm)*	212	8.3 (3.7)	226	8.3 (3.3)	0.01 (-0.65 to 0.67)	0.97
Super iliac skinfold thickness (mm)*	194	6.8 (3.4)	202	7.2 (4.14)	-0.40 (-1.15 to 0.34)	0.28
Abdomen skinfold thickness (mm)*	196	9.4 (4.8)	211	9.6 (4.2)	-0.20 (-1.06 to 0.66)	0.64
Sum of skinfolds (mm)*	185	39.8 (33.4 to 48.8)	196	42 (34.5 to 51.0)	-2.00 (-4.64 to 0.62)	0.13
Waist Circumference (cm)*	238	53.0 (4.5)	241	53.2 (4.2)	-0.16 (-0.92 to 0.60)	0.67
Mid upper arm circumference (cm)*	231	17.8 (1.6)	239	17.7 (1.9)	0.04 (-0.26 to 0.36)	0.76
BMI for age z-score*	236	0.88 (1.0)	249	0.88 (1.0)	0.004 (-0.18 to 0.19)	0.96
IOTF obese percentile	230	20 (8.8)	243	20 (8.2)	1.06 (0.55 to 2.04)	0.86
IOTF overweight or obese percentile	230	73 (31.7)	243	93 (38.3)	0.73 (0.50 to 1.08)	0.11
Body fat percentage calculated from BIA**	186	22.3 (7.1)	196	22.4 (6.1)	-0.30 (-1.62 to 1.01)	0.65
Pulse rate (bpm)**β	199	91 (20.0)	204	96 (17.4)	-4.8 (-8.41 to -1.07)	0.01
Systolic blood pressure percentile **	197	80 (63 to 91)	207	78 (63 to 90)	2.79 (-1.81 to 7.39)	0.23
Diastolic blood pressure percentile **	196	79 (57 to 91)	205	82 (64 to 88)	-2.98 (-7.76 to 1.08)	0.22

*Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; BPM: beats per minute; CI: confidence interval; IOTF: international obesity task force; IQR: interquartile range; mm, millimetres; cm, centimetres; kg, kilograms, SD, standard deviation. *Treatment effect adjusted for minimisation variables of randomisation maternal BMI, parity & ethnicity, child age at 3-year follow up and sex. *Z-scores calculated using WHO standards (de Onis , 2006)*

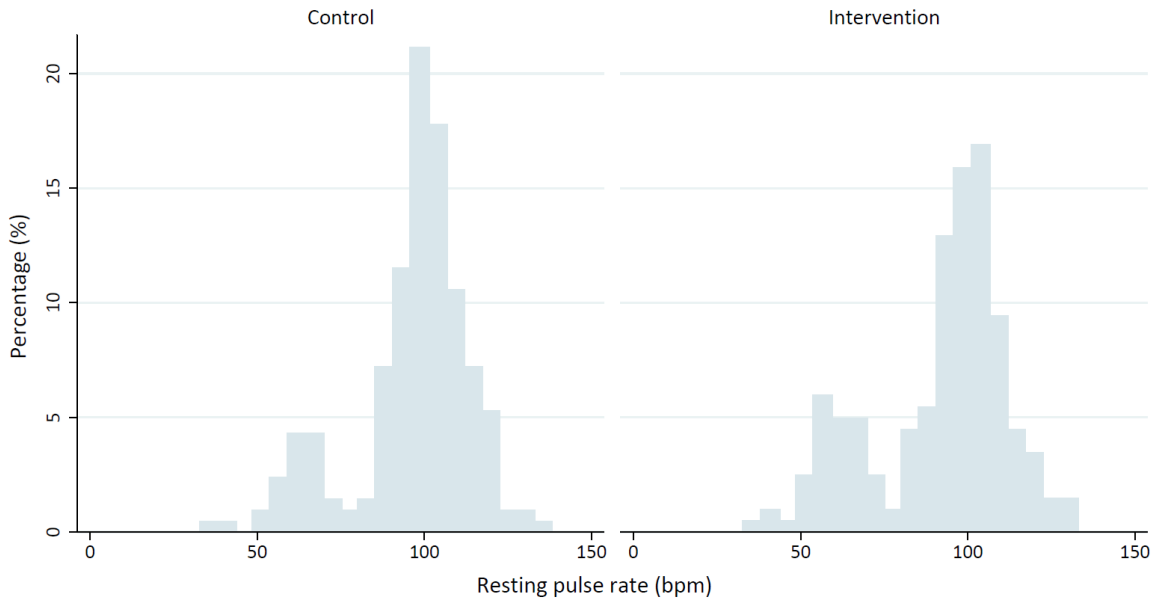
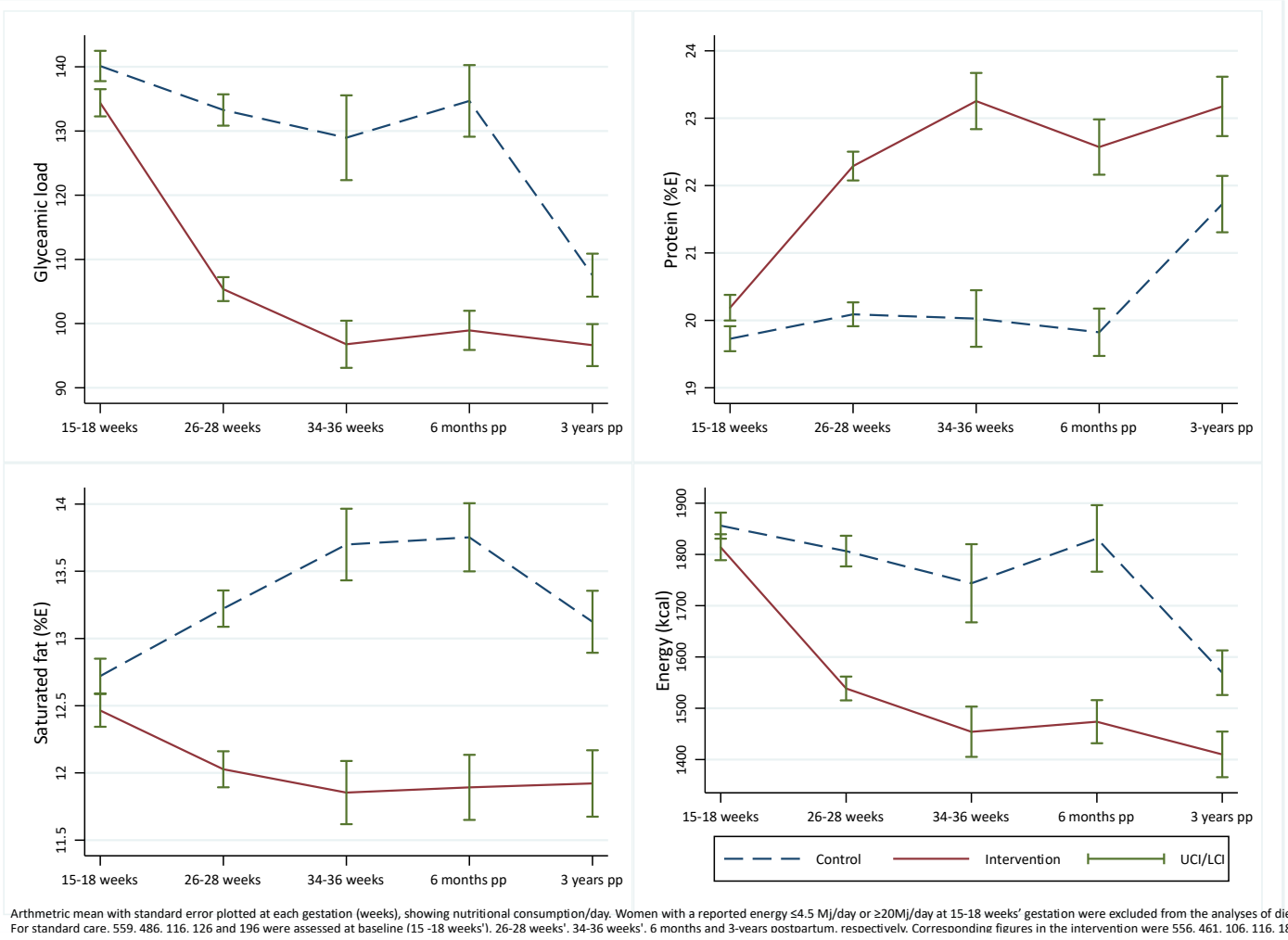


Figure 4:4: Resting pulse rate at 3-years of age, by randomisation arm



Arthmetric mean with standard error plotted at each gestation (weeks), showing nutritional consumption/day. Women with a reported energy ≤4.5 Mj/day or ≥20Mj/day at 15-18 weeks' gestation were excluded from the analyses of diet. For standard care, 559, 486, 116, 126 and 196 were assessed at baseline (15 -18 weeks'), 26-28 weeks', 34-36 weeks', 6 months and 3-years postpartum, respectively. Corresponding figures in the intervention were 556, 461, 106, 116, 185.

Figure 4:5: Maternal dietary intake for protein, energy and saturated fat, across pregnancy to 3 years postpartum, by randomisation arm.

Table 4:4: UPBEAT 3-year follow-up: Comparison of maternal characteristics of those who attended the 3-year follow-up versus those who did not, by randomisation arm.

Maternal		Followed-up					Not followed-up					Follow up vs not-follow-up
		Intervention		Control		Mean difference/ OR (95%CI)	Intervention		Control		Mean difference/ OR (95%CI)	
		Mean (SD)/ Median (IQR) N (%)					Mean (SD)/ Median (IQR) N (%)					
Age (years) at baseline		250	31.2 (5.0)	264	31.3 (5.5)	-0.09 (-1.01 to 0.82)	513	30.1 (5.6)	493	30.0 (5.5)	0.19 (-0.49 to 0.87)	0.0001
BMI (kg/m^2) at baseline		250	34.5 (32.5-38.0)	264	34.9 (32.6-37.8)	-0.14 (-0.96 to 0.68)	513	35.5 (32.8 -39.0)	493	35.4 (33.1 – 38.7)	0.11 (-0.47 to 0.70)	0.007
ethnicity	Asian	250	13 (5)	264	9 (3)	1.47 (0.61 to 3.52)	513	30 (6)	493	39 (8)	0.74 (0.45 to 1.23)	0.02
	Black		55 (22)		64 (24)	0.87 (0.57 to 1.32)		139 (27)		130 (26)	1.03 (0.77 to 1.36)	
	White		173 (69)		176 (67)	ref		309 (60)		299 (61)	ref	
	Other		9 (4)		15 (6)	0.61 (0.26 to 1.43)		35 (6)		25 (5)	1.35 (0.79 to 203)	
Multiparous		250	124 (50)	264	138 (52)	0.90 (0.63 to 1.27)	513	312 (61)	493	285 (58)	1.13 (0.88 to 1.45)	0.002
Smoking status at baseline		250	5 (2)	264	14 (5)	0.88 (0.56 to 1.38)	513	42 (8)	493	44 (9)	0.39 (0.13 to 1.11)	0.001
IMD quintiles*	1 (least deprived)	247	14 (6)	264	16 (6)	0.78 (0.36 to 1.68)	510	15 (3)	491	18 (4)	0.77 (0.38 to 1.55)	0.09
	2		21 (8)		15 (6)	1.24 (0.61 to 2.55)		35 (7)		29 (6)	1.11 (0.66 to 1.88)	
	3		28 (11)		30 (11)	0.83 (0.46 to 1.50)		59 (12)		54 (11)	1.00 (0.67 to 1.52)	
	4		75 (31)		106 (40)	0.63 (0.42 to 0.94)		165 (32)		172 (35)	0.88 (0.66 to 1.17)	
	5 (mot deprived)		109 (44)		97 (37)	ref		237 (46)		219 (44)	ref	
Sum of skinfolds (cm) at baseline		246	121.6 (29.5)	263	122.7 (25.7)	-1.15 (-5.97 to 3.66)	505	123.1 (28.0)	486	122.9 (26.7)	0.25 (-3.16 to 3.66)	0.57
Antenatal characteristics	GDM**	234	56 (24)	250	69 (27)	0.82 (0.55 to 1.24)	402	106 (26)	411	104 (25)	1.06 (0.77 to 1.45)	0.99
	PE¥	249	6 (2)	260	10 (4)	0.62 (0.22 to 1.72)	496	21 (4)	485	17 (4)	1.21 (0.63 to 2.33)	0.47
	Total GWG from 15-18 weeks¶	222	7.3 (4.5)	230	7.7 (4.2)	-0.38 (-1.17 to 0.42)	304	7.1 (4.6)	337	7.9 (4.7)	-0.76 (-1.50 to -0.04)	0.90

*Abbreviations: BMI, body mass index; CI, confidence intervals; GDM, gestational diabetes; GWG, gestational weight gain; IMD, indices of multiple deprivation; IQR, interquartile range; PE, pre-eclampsia; SD, standard deviation. *IMD quintiles are calculated for the region of residence, by fifths of the population. UK wide scores were developed by reconciling Scottish data to English norms. ** Gestational diabetes (GDM) diagnosis by International Association of Diabetes in Pregnancy Study Group criteria at 27^{+0} to 28^{+6} weeks' gestation. ¥ Pre-eclampsia defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both, on at least two occasions 4 hours apart, with proteinuria ≥300 mg/ 24 hours. ¶Total gestational weight gain calculated using estimated weight before pregnancy and weight at 36 weeks'.*

Table 4:5**:** UPBEAT 3-year follow-up: Comparison of neonatal characteristics of those who attended the 3-year follow-up versus those who did not, by randomisation arm.

		Follow up at 3 years					Not-follow up at 3 years					Follow up vs not-follow-up
		Intervention		Control		Mean difference/ OR (95% CI)	Intervention		Control		Mean difference/ OR (95% CI)	
		Mean (SD)/ N (%)					Mean (SD)/N (%)					
Birth characteristics	Gestation at birth (weeks)	250	39.8 (1.5)	264	39.5 (2.2)	0.25 (-0.07 to 0.58)	509	39.4 (2.2)	488	39.5 (2.1)	-0.15 (-0.42 to 0.11)	0.09
Anthropometry	Birthweight (grams)	250	3523 (526)	264	3426 (578)	97.2 (1.3 to 193.0)	509	3374 (605)	488	3457 (588)	-82.0 (-156.3 to -7.8)	0.06
	Birthweight >4kg	250	40 (16)	264	28 (11)	1.6 (0.95 to 2.69)	509	65 (13)	488	77 (16)	0.78 (0.54 to 1.11)	0.60
	LGA >90$^{th\,\dagger}$ Centile	250	39 (15)	264	25 (9)	1.76 (1.03 to 3.01)	509	57 (11)	493	59 (12)	0.91 (0.62 to 1.35)	0.64
	Subscapular skinfold thickness (mm)	113	5.7 (1.4)	113	5.5 (1.3)	0.24 (-0.13 to 0.61)	145	5.7 (1.5)	131	5.6 (1.4)	-0.07 (-0.41 to 0.28)	0.88
	Triceps skinfold thickness (mm)	115	5.3 (1.3)	119	5.2 (1.6)	0.08 (-0.30 to 0.47)	134	5.3 (1.4)	149	5.3 (1.5)	0.01 (-0.34 to 0.37)	0.64
Neonatal feeding history at 72 hrs	Formula feeding	249	47 (19)	264	53 (20)	0.91 (0.58 to 1.43)	503	128 (26)	478	109 (23)	1.17 (0.86 to 1.60)	0.04
	Breast feeding		158 (63)		163 (62)	Ref		270 (54)		271 (57)	Ref	
	Partially breastfeeding		44 (18)		48 (18)	0.94 (0.59 to 1.50)		105 (21)		98 (20)	1.07 (0.77 to 1.48)	

Abbreviations: CI, confidence intervals; LGA, large for gestational age; OR, odds ratio; SD, standard deviation. † Customised birthweight centile adjusting for maternal height and weight, ethnicity, parity and sex of the infant.

Table 4:6: UPBEAT 3-year follow-up: Maternal nutrition and physical activity outcomes from the UPBEAT trial, by gestation of evaluation

		Follow up at 3 years					
		Intervention		Control		Mean difference (95% CI) *	P-value
		Mean (SD)/ Median (IQR) N (%)					
	Gestation weight gain (kg)‡						
	Total	220	7.3 (4.5)	231	7.6 (4.2)	-0.40 (-1.20 to 0.40)	0.26
	Before pregnancy to 27-28 weeks + 6 days	231	5.1 (3.0)	250	5.2 (2.7)	-0.19 (-0.69 to 0.31)	0.36
Anthropometry	Sum of skinfolds (mm)§						
	27-28 weeks + 6 days	230	120.8 (25.8)	250	126.2 (27.1)	-5.44 (-10.2 to -0.7)	0.02
	34-36 weeks + 0 days	217	119.5 (24.4)	227	123.5 (27.5)	-3.96 (-8.8 to 0.9)	0.06
	Mid-arm circumference						
	27-28 weeks + 6 days	230	36.5 (4.0)	249	36.4 (4.2)	0.22 (-0.53 to 0.96)	0.38
	34-36 weeks + 0 days	220	36.59 (4.0)	231	36.32 (4.4)	0.26 (-0.52 to 1.04)	0.28
	Thigh circumference (mm)						
	27-28 weeks + 6 days	230	67.0 (6.7)	249	68.6 (7.0)	0.39 (-0.83 to 1.62)	0.30
	34-36 weeks + 0 days	220	68.9 (6.8)	231	69.0 (7.1)	-0.20 (-1.46 to 1.06)	0.78
Diet [a]	Total energy (MJ/day)						
	15-18 weeks + 6 days	184	7.4 (2.2)	199	7.7 (2.4)	-0.29 (-0.75 to 0.18)	
	27-28 weeks + 6days	167	6.5 (1.7)	192	7.4 (2.2)		<0.0001
	Glycaemic Index (0-100)						
	15-18 weeks + 6 days	184	56.8 (4.0)	199	56.6 (4.2)	0.15 (-0.66 to 0.96)	
	27-28 weeks + 6days	167	54.4 (3.9)	192	57.0 (3.7)	-2.62 (-3.40 to -1.85)	<0.0001
	Glycaemic Load						
	15-18 weeks + 6 days	184	128.8 (41.0)	199	136.6 (54.1)	-7.84 (-17.52 to -1.86)	
	27-28 weeks + 6days	167	103.9 (29.7)	192	129.8 (45.1)	-4.09 (-17.8 to -33.9)	<0.0001
	Carbohydrates (% Energy)						
	15-18 weeks + 6 days	184	48.7 (7.5)	199	49.0 (7.2)	-0.26 (-1.74 to 1.22)	
	27-28 weeks + 6days	167	46.1 (6.2)	192	48.2 (6.2)	-2.12 (-3.44 to -0.80)	<0.0001
	Protein (% Energy)						
	15-18 weeks + 6 days	184	20.4 (4.4)	199	19.8 (4.3)	0.62 (-0.26 to 1.50)	

	27-28 weeks + 6days	167	22.9 (4.3)	192	20.3 (4.0)	2.64 (1.8 to 3.5)	<0.0001
	Total fat (% energy)						
	15-18 weeks + 6 days	184	30.94 (5.5)	199	31.34 (5.7)	-0.43 (-1.52 to 0.65)	
	27-28 weeks + 6days	167	30.78 (4.9)	192	31.69 (5.0)	-0.91 (-1.95 to 0.12)	0.47
	Saturated fat (g/day)						
	15-18 weeks + 6 days	184	24.70 (10.6)	199	26.50 (11.6)	-1.80 (-4.03 to 0.43)	
	27-28 weeks + 6days	167	21.40 (7.8)	192	26.34 (10.5)	-4.94 (-6.88 to -3.00)	<0.0001
	Saturated fat (% energy)						
	15-18 weeks + 6 days	184	12.5 (2.8)	199	12.9 (3.0)	-0.45 (-1.03 to 0.13)	
	27-28 weeks + 6days	167	12.2 (2.7)	192	13.3 (2.8)	-1.06 (-1.63 to -0.49)	0.018
	Fibre (g/day)						
	15-18 weeks + 6 days	184	13.0 (4.5)	199	13.4 (5.2)	-0.48 (-1.48 to 0.498)	
	27-28 weeks + 6days	167	12.9 (4.6)	192	12.5 (4.3)	0.40 (-0.52 to 1.33)	0.25
Physical Activity [b]	MET (min/week)						
	15-18 weeks + 6 days	218	1335 (495-3630)	234	1386 (693-3108)		
	27-28 weeks + 6days	205	1584 (693-4026)	220	1313 (615-3249)	394.2 (66.6 to 721.9)	<0.0001
	Walking (min/week)						
	15-18 weeks + 6 days	218	242 (120- 560)	234	280 (140- 630)		
	27-28 weeks + 6days	205	360 (150-840)	220	240 (120- 585)	99 (23 to 175)	0.01

*Abbreviations: CI, Confidence interval; IQR: interquartile range; MET, metabolic equivalent of task; MJ: millijoules; OR, odds ratio SD: standard deviation. [‡] Gestational weight gain calculated using estimated weight before pregnancy.[§] Calculated by addition of biceps, triceps, suprailiac, and subscapular skinfold thicknesses. [a] Women with reported total energy ≤4·5 MJ/day or ≥20 MJ/day at 15–18 weeks + 6 days of gestation were excluded from analyses of diet. Thus, in the standard care group, 199 women were assessed at 15–18 weeks + 6 days of gestation and 192 were assessed at 27–28 weeks + 6 days of gestation; corresponding figures in the intervention group were 184 and 167. For analyses of physical activity, in the standard care group, 234 women were included at 15–18 weeks + 6 days of gestation and 220 were assessed at 27–28 weeks + 6 days of gestation; in the intervention group, 184 and 167 women, respectively, were analysed. [b] Physical activity estimates were calculated by bootstrapped (1000 replications) median regression, adjusting for pretrial values. MET is defined as the energy expenditure ratio of activity to rest; one MET is roughly equal to an individual's resting energy expenditure. MET, vigorous activity, moderate or vigorous activity, and walking were not prespecified endpoints. *Treatment effect adjusted for maternal BMI, parity and ethnicity.*

Table 4:7: UPBEAT 3-year follow-up: Maternal diet measured at 3 years postpartum, by randomisation arm

Maternal Diet [b]		Intervention Mean (SD)		Control Mean (SD)	Mean difference (95%CI) [a]	P-value
Energy (kcal)	152	1645 (559)	195	1716 (549)	-69.7 (-187 to 47)	0.244
Protein (%E)	152	23.5 (5.2)	195	21.5 (5.1)	1.99 (0.88 to 3.09)	<0.001
Total Fat (%E)	152	31.0 (5.7)	195	32.7 (5.0)	-1.57 (-2.69 to -0.457)	0.006
Saturated Fat (%E)	152	11.6 (2.8)	195	12.7 (2.8)	-1.10 (-1.66 to -0.50)	<0.001
Carbohydrate (%E)	152	45.5 (7.9)	195	45.9 (7.4)	-0.42 (-2.02 to 1.18)	0.605
Fibre (NSP) (g)	152	13.8 (6.6)	195	13.3 (5.4)	0.69 (-0.59 to 1.97)	0.293
Glycaemic Load	152	113 (45.8)	195	121 (46.7)	-8.43 (-18.14 to 1.23)	0.089
Glycaemic Index	152	56.6 (3.7)	195	57.5 (3.8)	-0.96 (-1.77 to -0.15)	0.019
Total Sugars (%E)	152	19.8 (8.0)	195	20.0 (7.6)	-0.16 (-1.80 to 1.47)	0.842
Maternal physical activity [c]		Median (IQR)		Median (IQR)	Median regression (95% CI) [a]	
MVPA (min/week)	125	195 (105 to 360)	121	190 (120 to 390)	0.00 (-49.57 to 49.57)	1.000
MET (min/week) [d]	225	1884 (1017 to 3465)	240	1719 (990 to 3243)	40.31 (-443.69 to 524.31)	0.870
Walking (min/week)	215	420 (160 to 840)	235	420 (150 to 630)	0.27 (-71.32 to 71.86)	0.994

Abbreviations: CI, confidence intervals; % E, % energy; MET, metabolic equivalent of task; MVPA, moderate and vigorous physical activity. [a] Treatment effect adjusted for maternal BMI, parity and ethnicity. [b] Maternal diet—women with a reported energy ⩽4.5 MJ per day or ⩾20 MJ per day were excluded from the analyses of diet. [c] Physical activity estimates were calculated using bootstrapped (1000 replications), median regression adjusting for minimization variables and maternal pre-pregnancy current smoking status. [d] MET is defined as the energy expenditure ratio of activity to rest; one MET is approximately equal to an individual's resting energy expenditure.

Table 4:8: UPBEAT 3-year follow-up: Maternal anthropometry measured at 3 years postpartum, by randomisation arm

	Intervention		Control		Mean difference (95% CI) [a]	p-value
	Mean (SD)/ Median (IQR) N (%)					
Subscapular (mm)	224	35 (9.6)	241	36 (10.5)	-0.07 (-2.01 to 1.81)	0.96
Triceps (mm)	225	33 (9.4)	241	34 (8.4)	-0.56 (-2.32 to 1.20)	0.56
Biceps (mm)	225	22 (8.4)	241	22 (7.6)	-0.51 (-2.18 to 1.15)	0.50
Suprailiac (mm)	225	31.5 (11.9)	240	31.0 (10.2)	-0.60 (-2.40 to 1.14)	0.36
Sum of skinfolds (mm)	224	121 (29.5)	240	122 (25.6)	-1.72 (-7.30 to 3.81)	0.48
Mid upper arm circumference (cm)	226	36.4 (5.1)	240	36.1 (4.9)	0.23 (-0.67 to 1.13)	0.42
Waist circumference (cm)	226	105 (13.5)	241	105 (13.1)	0.18 (-2.24 to 2.60)	0.78
Weight (kg)	227	95.8 (85.8 - 109)	241	96.2 (85.8 – 107.5)	0.77 (-2.54 to 4.07)	0.65
Thigh circumference (cm)	226	66.9 (7.3)	241	66.7 (7.2)	0.17 (-1.14 to 1.50)	0.52

Abbreviations: BMI, Body mass index; CI, confidence intervals; cm: centimetres; IQR: interquartile range; kg, kilograms; mm: millimetres; SD, Standard Deviation. [a] Treatment effect adjusted for maternal BMI, parity and ethnicity. Women who were pregnant at 3-year visit or had given birth with the previous 4 months were excluded.

Table 4:9: Multiple imputation of the effect of the UPBEAT intervention on childhood outcomes at 3-years of age

	Observations	Missing data	% missingness	Effect size using MI*	p-value
Weight (kg)*	503	1017	66	0.14 (-0.37 to 0.65)	0.57
height (cm)*	502	1018	66	0.29 (-0.49 to 1.08)	0.45
Subscapular (mm)*	424	1096	72	0.15 (-0.69 to 0.99)	0.70
Triceps (mm)*	450	1070	70	0.25 (-0.35 to 0.87)	0.40
Biceps (mm)*	444	1076	70	0.06 (-0.58 to 0.71)	0.83
Super iliac (mm)*	401	1119	73	-0.05 (-0.69 to 0.57)	0.85
Abdomen (mm)*	412	1108	72	0.07 (-0.63 to 0.78)	0.84
Sum of skinfolds (mm)*	386	1134	71	-1.02 (-4.38 to 2.32	0.54
Waist circumference (cm)*	488	1032	67	-0.03 (-0.79 to 0.72)	0.93
MUC circumference (cm)*	479	1041	68	0.08 (-0.25 to 0.42)	0.60
BMI for age z-score*	494	1026	67	0.03 (-0.19 to 0.26)	0.78
Body fat percentage **	388	1132	74	-0.41 (-1.78 to 0.95)	0.53
Pulse rate (bpm)**[8]	409	1111	73	-4.88 (-8.7 to -0.98)	0.01

*Abbreviations: bpm: beats per minute; mm: millimetres; cm: centimetres; kg: kilograms, MI: multiple imputation, MUC: Mid-upper arm. *Treatment effect adjusted for minimisation variables of randomisation maternal BMI at baseline, parity & ethnicity, child age at 3-year follow up and sex. Data was imputed to create 50 datasets, using 10 burn-in iterations for all live-born infants (n=1520), using the following maternal demographic characteristics: maternal BMI (at baseline), age, ethnicity, parity, GDM diagnosis, centre of treatment, mode of feeding on hospital discharge. Analysis was performed by intention to treat; treatment effects were estimated using mean difference (as all outcomes were continuous).*

4.5 Discussion

To our knowledge this study of 514 pre-school children born to mothers with obesity randomised to a lifestyle intervention in pregnancy is the largest to be reported to date. In a previous analysis of the UPBEAT infants at 6 months of age, we reported a reduction in subscapular skinfold thickness, a measure which, in adults, is associated with risk of metabolic disease (Patel et al., 2017a). In this study we have shown that at 3-years of age this effect was not sustained, despite trends towards lower adiposity and a lower incidence of overweight/obesity.

Although there are many reports of the consequences of maternal obesity on offspring health from animal (Menting et al., 2019) and cohort studies (Davey Smith et al., 2007; Heslehurst et al., 2019) very few have addressed the influence of an antenatal intervention beyond infancy, as we reported recently in a systematic review (Dalrymple et al., 2018b). The only study in children of a similar age, Tanvig et al, reported no effect on offspring body composition of the antenatal intervention (diet and physical activity), in 2.8-year-old children despite a reduction in maternal GWG. In conjunction with our 6-month (Patel et al., 2017a) outcome data, these data may suggest that such effects may diminish in the children over time. One caveat in interpreting our findings is the potential for the so-called "adiposity rebound" to obfuscate effects of the intervention on adiposity at age 3.5 years, particularly important as an early adiposity rebound is associated with later obesity risk; follow up at an older age when all children are past the adiposity rebound would be of interest.

However, common to all studies is the modest effect of the lifestyle interventions in the mothers on measures of gestational weight gain, adiposity and health outcomes. This is highlighted by an individual participant meta-analysis of 36 antenatal lifestyle RCTs in weight heterogeneous pregnant women which concluded that recommendations for improved diet and physical activity caused a mean reduction of -0.7kg (-0.92, -0.48) GWG. A lower caesarean section rate was the only evidence of improved clinical outcome (i-WIP Collaborative Group, 2017). The remarkably strong relationship between maternal obesity and childhood obesity (Castillo et al., 2015; Heslehurst et al., 2019) could result from shared obesogenic genes, or shared family environment or a persistent influence of in utero exposures on the developing fetus, or a combination of all of these. Clearly, to address the latter explanation, maternal interventions which substantially affect the maternal phenotype and metabolic health are required before conclusions can be reached as to the

relative contributions of these possible determinants. Behavioural change interventions have yet to prove effective. Future strategies may include targeted behavioural interventions in women stratified as higher risk, and/or including a combination of personalised coaching with supporting mobile technology (O'Brien et al., 2014). However, optimising BMI before pregnancy is now seen as a more achievable target for intervention which would not only reduce the complications of a higher BMI in pregnancy but also contribute to improve gamete and early embryonic development (Stephenson et al., 2018).

This study, for the first time, has found that a dietary and physical activity intervention in pregnant women with obesity was associated with a reduction in the resting pulse rate of their 3-year-old children. In adults, increased resting pulse rate has been associated with hypertension and cardiovascular dysfunction (Nanchen et al., 2013). Of the few reports in children, a high resting pulse rate has been linked to obesity and increased blood pressure (Voors et al., 1982). Resting pulse rate in children has also been reported to be inversely related to physical activity (Cordova et al., 2012), however we found no association with the parent-reported activity and sedentary time of their child and resting pulse rate at 3-years of age.

An association between maternal obesity and offspring cardiometabolic dysfunction has also been strongly suggested in experimental animals (Samuelsson et al., 2008, 2010, 2013; Menting et al., 2019). In these studies, maternal obesity has been related to a sustained increase in offspring central sympathetic activity at the level of the hypothalamic neuronal pathways. This has been implicated in an observed rise in blood pressure in the offspring and also to altered heart rate variability (Samuelsson et al., 2010). Our data could support a similar association between obese women and their children, and prompts further and more detailed investigation in UPBEAT children at an older age. This should include an assessment of heart rate variability through pulse wave analysis, a method which enables determination of parasympathetic and sympathetic pathways of the autonomic nervous system (ANS) (Ernst, 2017). It is of interest and potential relevance that studies of maternal overnutrition in rodents have reported epigenetic marks in central pathways which may be associated with peripheral autonomic regulation (Samuelsson et al., 2010; Taylor et al., 2014; Ramamoorthy et al., 2018).

The bimodal distribution of heart rate observed in the whole cohort of children was unrelated to maternal dietary intake or resting pulse rate, child's diet, weekly activity and sedentary time, time of day, seasonality or centre of measurement (heart rate monitoring device) and was not influenced by potential outlier data. To our knowledge this clear bimodal distribution has not been previously reported. Therefore, there is no inference that this bimodal distribution reflects two groups of active and inactive children and its origin remains unknown.

It was of interest that the effect of the intervention in terms of improvements in maternal diet was maintained to 3-years, having previously been demonstrated at 6 months (Patel et al., 2017a). This finding supports the theory that pregnancy is a 'teachable' moment for initiating longer-term improvements in dietary intake (Phelan, 2010).

4.5.1 Strengths and limitations

Trained research midwives/assistants conducted all the follow-up appointments using detailed standard operating procedure and a database that incorporated data queries from research staff, therefore reducing the risk of error or missing data. Further strengths of the study include the prospective collection of in-depth data of pregnancy demographic, health, metabolic and lifestyle variables and individual determinants of childhood body composition and health outcomes, allowing for adjustment of potential confounders. The main limitation of this study is the follow-up of only 33% of those eligible from the original RCT (Poston et al., 2015), which may have resulted in selection bias. The differences by randomised group in maternal characteristics between those lost to follow-up and those followed and included in analyses here suggest this might be apparent in this data. Furthermore, the difference in resting pulse rate was a secondary outcome. Therefore, replication of that finding, ideally in another large RCT with minimal loss to follow-up is important for validation. Although the mothers who returned at 3-years were generally representative of the main trial population, there was a higher proportion of LGA infants in the intervention arm which may have influenced body composition at 3-years of age, as infants born large for gestational age have been shown to retain a higher BMI throughout childhood and adolescence (Geserick et al., 2018).

Methods used to assess body composition of the children are indirect methods for assessing distribution of fat mass and future studies should consider using dual-energy x-ray

absorptiometry (DXA). However, in older children and adolescents high correlations between DXA assessed total fat mass and BMI have been demonstrated and the associations of BMI and DXA fat mass with lipids, markers of insulin a liver fat in those children and adolescents are identical, suggesting BMI is a good a marker of metabolic risk in children (Dangardt et al., 2019). A further limitation is the use of self-reported FFQ for the dietary intake in the mothers, although, during the pilot for UPBEAT the food frequency questionnaire performed favourably against a more rigorous methods for dietary assessment (Poston et al., 2013).

In conclusion, this study provides some evidence that improving the antenatal environment in women with obesity may have a positive effect on the cardiovascular health for their offspring. Although there was no impact of the antenatal intervention on adiposity of their child, obesity in pregnancy remains a prominent factor in the proliferation of the intergenerational cycle of obesity (Heslehurst et al., 2019). It is of critical importance to develop interventions in high-risk maternal populations which may have profound clinical and metabolic consequences on the mother to determine an in utero influence on subsequent obesity and cardiovascular risk in the offspring. Further investigation of the UPBEAT children when past the nadir of the "adiposity rebound", and analysis of cardiovascular function and body fat deposits will provide additional insight into any longer-term consequences of the intervention.

Chapter 5 Associations between dietary patterns, eating behaviours and body composition and adiposity in 3-year old children of mothers with obesity

Publications based on this chapter:

Dalrymple KV, Flynn AC, Seed PT, Briley AL, O'Keeffe M, Godfrey KM and Poston L. Associations between dietary patterns, eating behaviours and body composition and adiposity in 3-year old children of mothers with obesity. *Pediatric Obesity*. 2019.

5.1 Abstract

Background: The relationships between eating habits, behaviours and the development of obesity in pre-school children is not well established.

Objective: As children of mothers with obesity are themselves at risk of obesity, we examined these relationships in a cohort of 482 three-year-old children of mothers with obesity from the UPBEAT study.

Method: Dietary patterns were derived using factor analysis of an 85-item food frequency questionnaire (FFQ). Eating behaviours were assessed using the Children's Eating Behaviour Questionnaire (CEBQ). Measures of body composition included age-specific BMI cut-offs, WHO z-scores, sum of skinfolds, waist and arm circumferences and body fat percentage. Using adjusted regression analysis, we examined associations between dietary patterns, eating behaviours and measures of body composition.

Results: Three distinct dietary patterns were defined; "healthy/prudent", "African/Caribbean" and "processed/snacking". The "processed/snacking" pattern was associated with greater odds of obesity; OR 1.53 (95%CI: 1.07 to 2.19). The "African/Caribbean" and the "healthy/prudent" patterns were associated with a lower arm circumference (β=-0.23cm (-0.45 to -0.01)) and sum of skinfolds (β=-1.36cm (-2.88 to -0.37)), respectively. Lower enjoyment of food and food responsiveness, and greater slowness in eating and satiety, were associated with lower arm and waist circumferences, WHO z-scores and obesity (all $p<0.05$).

Conclusion: In children of mothers with obesity, those who had higher scores on a "processed/snacking" dietary pattern had greater odds of obesity. In contrast slowness in eating was associated with lower measures of body composition. These novel findings highlight modifiable behaviours in high-risk pre-school children which could contribute to public health strategies for prevention of childhood obesity.

5.2 Introduction

Recent figures from the National Child Measurement Programme in England suggest that nearly a quarter of pre-school children have overweight or obesity (NHS, 2015), with one in 40 children being affected by severe obesity. Obesity in early life is a predictor for adolescent and adulthood obesity (Druet and Ong, 2008; Singh et al., 2008; Geserick et al., 2018), with a recent meta-analysis of 37 studies reporting that children classified as having obesity using body mass index (BMI) were five-times more likely to have obesity as adults compared to their healthy weight counterparts (Simmonds et al., 2016). Worldwide, there is intense focus on reducing rates of childhood obesity (World Health Organisation, 2016; UK Government: Department of Health and Social Care, 2018). The UK government recommend creating healthier food environments in schools, local areas and providing parents with information on healthy food choices for their families with the aim of halving rates of childhood obesity by 2030 (UK Government: Department of Health and Social Care, 2018).

Several studies have independently suggested a relationship between eating behaviours (Spence et al., 2011; Eloranta et al., 2012; van Jaarsveld et al., 2014; McCarthy et al., 2015) or dietary intake (Fernández-Alvira et al., 2017; Wolters et al., 2018) and body composition in childhood. Associations between weight status in early life and food approach eating behaviours, such as food responsiveness and emotional overeating and consumption of energy dense foods have consistently been reported. Longitudinal studies suggest that eating habits and food choices established in childhood are likely to persist into adulthood (Skinner et al., 2002; Nicklaus et al., 2005; Birch et al., 2007; Northstone and Emmett, 2008; Schwartz et al., 2011). Therefore, the early years provide a unique opportunity to develop and establish healthy eating habits and behaviours.

Since current guidelines for prevention of childhood obesity recommend identification of populations at risk and early engagement (World Health Organisation, 2016; UK Government: Department of Health and Social Care, 2018), we have addressed relationships between dietary habits and behaviours and childhood adiposity in children born to mothers with obesity. As recently reported by ourselves in a contemporary cohort (Dalrymple et al., 2019a), and previously in many mother-child cohort studies, children of mothers with obesity are at high-risk of developing obesity themselves (Heslehurst et al., 2019).

The primary aims of this study were to investigate 1) associations of childhood dietary patterns with measures of body composition and 2) associations between child's eating behaviours and measures of body composition in the 3-year old children born to mothers from inner city settings and ethnically diverse backgrounds from the UK Pregnancy Better Eating and Activity Trial (UPBEAT). The role of socio-economic deprivation in these relationships was also examined.

5.3 Methods

UPBEAT was a randomised controlled trial which explored the effect of an intensive 8-week antenatal diet and physical activity intervention in 1,555 women with a BMI ≥30kg/m^2 (Poston et al., 2015). The intervention focused on improving insulin sensitivity through reducing dietary glycaemic load, saturated fat intake, and increasing physical activity in comparison to standard antenatal care. The participants were from UK inner-city settings of ethnic diversity and high socioeconomic deprivation. Details of the intervention inclusion and exclusion criteria have been published previously (Briley et al., 2014; Poston et al., 2015).

The intervention had no effect on the primary outcomes of gestational diabetes and large for gestational age infants. However, it was effective at improving maternal dietary intake, reducing gestational weight gain and sum of skinfolds and increasing self-reported physical activity by 36 weeks' gestation (all $p \leq 0.04$). In the infants at 6-months of age we have reported that the intervention was associated with a reduction in a measure of adiposity (Patel et al., 2017a); as a cohort analysis in these infants, we have also shown positive associations between measures of appetite, assessed by the Baby Eating Behaviour Questionnaire, and body fat percentage, weight and growth (Patel et al., 2018).

Between August 2014 and October 2017 participants in the UPBEAT study were invited to attend a 3-year post-delivery visit with their children. The study design and protocol of the follow-up were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 13/LO/1108). The children were included in this analysis if they had 1) attended the follow-up visit at 3-years of age; 2) had eating behaviour and food frequency questionnaires completed by the main caregiver; and 3) had body composition data recorded during the 3-year visit. Children were excluded if they were suffering from severe illness or if they were born before 34 weeks' gestation.

5.3.1 Child variables

5.3.1.1 Food Frequency Questionnaire

The child's diet was assessed using an 85-item Food Frequency Questionnaire (FFQ). The list of food and drink items were compiled from the 80-item validated Southampton Women's Survey FFQ (Jarman et al., 2014). In addition, three questions were extended to include culturally appropriate options, e.g. "Rice-boiled & fried" extended to "Rice-boiled & fried

jollof, rice and peas". Five extra food items were included which were culturally appropriate for the non-white ethnic subgroups in the UPBEAT cohort (Black – including Afro Caribbean and African) Table 2:10, Box 2.4). The FFQ asked how often in the last three months the child had consumed each item with response options including: never, less than once per month, 1-3 times per month, number of times per week (1-7) or more than once per day. If the item was consumed more than once a day, the number of times was recorded. Food and drink items consumed more than once a week which were not included in the FFQ were recorded as additional items. Type of milk consumed as a drink or added to cereal and sugar added to drinks and cereal was also collected.

Dietary patterns of the children were derived using factor analysis. Food and drink items listed in the FFQ were categorised into 39 groups based on similar nutritional composition. On the basis of frequency consumption, three items recorded as additional foods were also included: porridge/shredded wheat, fast food (McDonalds, Burger King and KFC) and cereal bars (Table 2:10). Factor analysis with orthogonal varimax rotation was performed to derive the patterns using the children's weekly standardised frequency of each of the 39 food groups. The number of factors retained was chosen using the scree plot of eigenvalues. Within each factor, food groups with a factor loading coefficient ≥ ± 0.22 were chosen (Table 5:*9*); this cut-off was selected so that each dietary pattern had equal distribution of food groups. Food groups with a factor loading coefficient ≥ ±0.32 were considered to have a strong association with that factor. Derived dietary pattern labels were selected based on foods with the highest factor loadings (≥ ±0.32).

5.3.1.2 Child Eating Behaviour Questionnaire

The Child Eating Behaviour Questionnaire (Wardle et al., 2001) (CEBQ) is a validated parent-reported psychometric method to assess child's eating style and behaviour (Carnell and Wardle, 2007). The questionnaire consists of 35 items divided into eight eating behaviours, further sub-divided into food approach and food avoidance questions rated on a 5-point Likert scale (Never=1, Rarely=2, Sometimes=3, Often=4, Always=5) Seven reverse scoring questions. Food approach behaviours include food responsiveness, emotional over-eating, enjoyment of food and desire to drink; food avoidance behaviours were satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness. Higher scores indicate a higher level for the respective eating style.

5.3.1.3 Anthropometric measures and body fat percentage

The outcomes of interest for the offspring were measures of body composition and adiposity assessed by sum of skinfold thicknesses (addition of triceps, biceps, subscapular, suprailiac and abdominal skinfolds, measured in triplicate by trained research staff using children's Holtain skinfold callipers), mid-upper arm and waist circumferences, body fat percentage assessed by ImpediMed Imp SFB7 bioelectrical impedance analysis (BIA) and weight, height and BMI z-scores derived using the World Health Organisation (WHO) reference data (de Onis, 2006). Childhood obesity was defined by International Obesity Task Force (IOTF) sex-specific centiles (boys obesity = 98.9th centile and girls obesity = 98.6th centile) (Cole and Lobstein, 2012).

5.3.2 Maternal variables

We also addressed relationships between maternal social and demographic variables (maternal age at trial entry, ethnicity, socioeconomic status, years in full-time education and early-pregnancy BMI) and offspring eating habits.

5.3.3 Statistical analysis

In this secondary analysis of the UPBEAT study there was no effect of the intervention on offspring eating patterns or behaviours, therefore the data was treated as a cohort. Demographic results were expressed as mean ± standard deviation, median and interquartile range or percent and number as appropriate. Depending on the outcome of interest, unadjusted and adjusted linear, logistic or quantile regression were used. Unadjusted regression (model 1) was performed to analyse the relationship between maternal social and demographic factors and dietary patterns at age 3-years, followed by adjusted regression (model 2) to investigate the relationship of the derived dietary patterns and the eight CEBQ subscale scores with the nine measures of body composition at age 3-years. For model 2 confounding variables (summarised in Table 5:1) were selected due to their association with dietary intake and body composition and included the minimisation variables from the main trial (maternal BMI at trial enrolment, parity and ethnicity), smoking status at baseline, maternal age, years spent in full time education, infant birthweight, child's age at follow-up, sex and randomisation arm. Coefficients or odds ratios were presented with 95% confidence

intervals. Data was analysed using Stata software, version 15.0 (StataCorp, College Station, Texas).

Table 5:1: Description and reasoning behind potential confounders

Confounder	Definition	Reasoning
Maternal age	Continuous	Lower maternal age has been associated with lower diet quality in children (Marvin-Dowle et al., 2018)
Maternal BMI	Continuous	Children born to overweight or obese mothers have been reported to have lower diet quality and higher energy intake (Pei et al., 2014)
Parity	Binary; 0-Nultip (reference), 1-Multip	Parity has previously been associated with food avoidance eating behaviours, including food fussiness and picky eating (Emmett et al., 2018)
Maternal socioeconomic status	Categorical; 1-5, 5 (most deprived, reference).	Dietary patterns in early childhood have consistently been associated with maternal socio-economic status. With prudent, or a healthier dietary intake being associated with a higher maternal SES (Hidaka et al., 2016)
Maternal ethnicity	Categorical; 0-White (reference), 1-Black, 2-Asian, 3-Other	Maternal ethnicity influences the immediate familial environment subsequently influencing feeding practices within the household (Robinson et al., 2007)
Maternal educational attainment	Continuous; total years	Educational attainment is an indicator of parental social class. Observational studies have identified a dose response relationship between educational attainment and childhood obesity (Lamerz et al., 2005)
Smoking status at baseline	Categorical; never smoked (reference), current smoker, ex-gave up before pregnancy, ex gave up in pregnancy	Children of non-smokers consumed a diet that conforms more closely to current guidelines on healthy eating compared to smoking mothers (Rogers et al., 2003).
Birthweight	Continuous: weight in grams	Size at birth is a known predictor of later obesity throughout the life course (Cunningham et al., 2014). Children with higher birthweights have previously been shown to have larger appetites and have greater enjoyment of food and is associated with obesity-inducing eating behaviour (Ester et al., 2019; Oliveira et al., 2015)
Child sex	Categorical; Male, Female	Sex differences have been reported between eating behaviours, including food intake and appetite traits. (Keller et al., 2019)
Child age at follow-up	Continuous; age in months	Eating behaviours, including food rejection, such as picky/fussy eating and food neophobia are common between the age of 2- 6 years (Cooke et al., 2003; Lafraire et al., 2016). Food neophobia is thought to rise rapidly at 2 years of age and gradually decrease thereafter. Adjustment was made to account for age-related differences in eating habits.

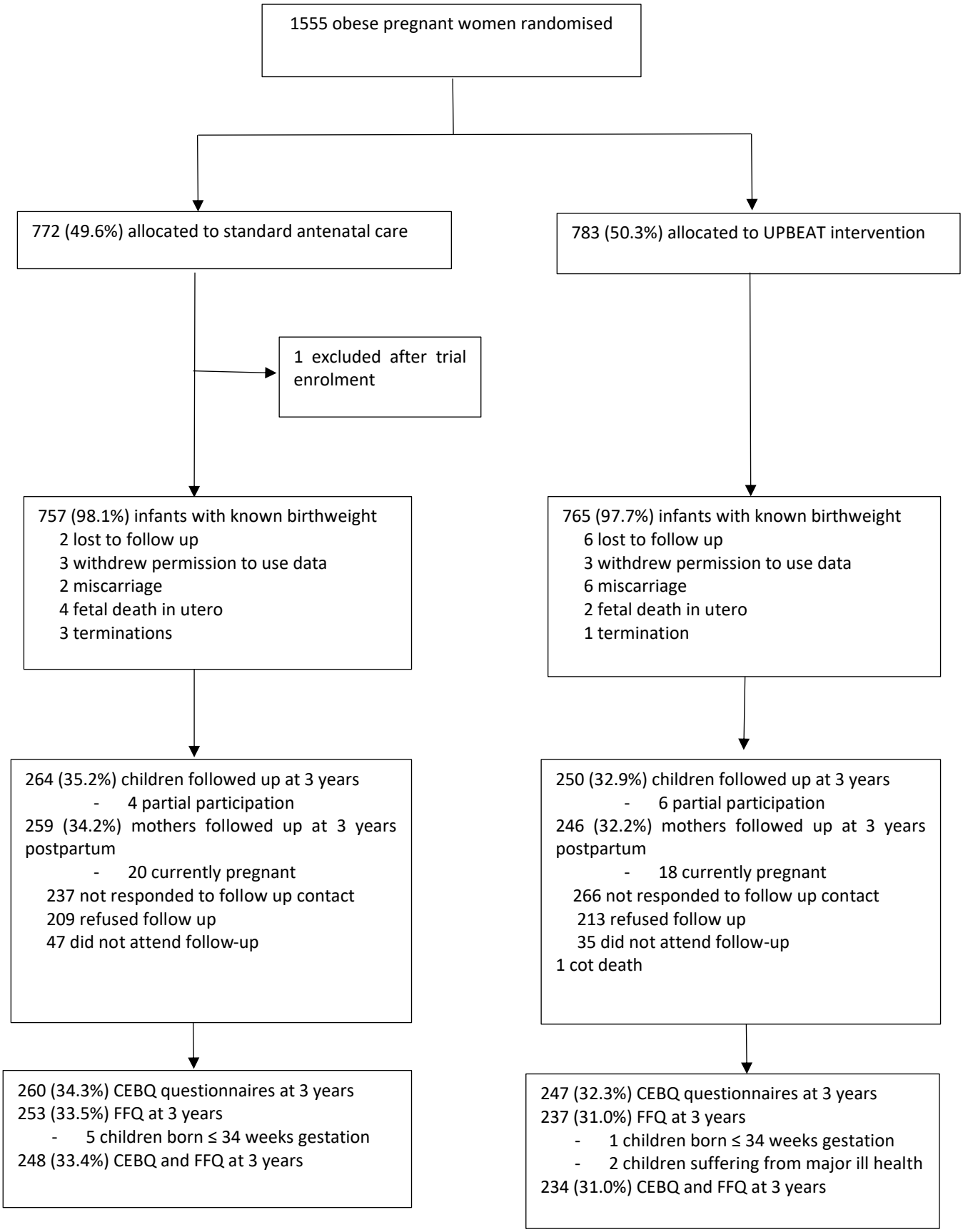


Figure 5:1: Consort diagram of participants enrolled in the UPBEAT trial at 3-years postpartum

5.4 Results

Figure 5:1 shows a flow chart of participants through the study. 514 children (33.0% of the original UPBEAT cohort) were followed up at age 3-years (3.5±0.28 years). 490 (95%) provided complete dietary data (FFQ and CEBQ), eight children were excluded as they were either born ≤34 weeks gestation or were suffering from severe illness, therefore the study population comprised of 482 children. Data for the majority of measures of anthropometry had less than 5% missingness except for BIA (20%) and sum of skinfolds (23%). Of the 482 included children, 243 (50%) were female and 234 (49%) were born to mothers who were randomised to the UPBEAT intervention arm. Mean maternal age was 31.2±5.2 years; 68% were White, 23% were Black African/Caribbean and 9% were from Asian or other ethnic backgrounds. 76% were from the index of multiple deprivation quintiles 4 and 5 (most deprived) Table 5:*2* . 165 of the children (34%) were overweight or had obesity, and 6% were morbidly obese (defined using the IOTF sex specific centiles (Cole and Lobstein, 2012)). For the WHO z-scores, the average height-for-age, weight-for-age and weight-for-height were above the mean of the reference population 0.38±1.1, 0.83±1.0 and 0.90±1.0, respectively (Table 5:*3*). Average energy intake for the children was 954 kcal (260) per day, with protein, saturated fats and carbohydrates contributing to 16.3%, 15.4% and 53.2% of energy respectively Table 5:*3*.

5.4.1 Dietary pattern analysis

Factor analysis identified three dietary patterns in the children, summarised in Figure 5:*2* with the list of factor loadings (≥±0.1) shown in Table 5:*9*. The first dietary pattern was labelled 'healthy/prudent' due to high loadings (≥0.32) on brown bread, boiled and baked potatoes, rice and pasta, fish, vegetables, beans and pulses, fruit (fresh, tinned and dried) and nuts. The second dietary pattern was characterised as a diet high in white bread, crisps and savoury snacks, roast potatoes (including chips), processed foods, quiche and pizza, confectionary, desserts, cakes, biscuits and low and high sugary drinks and this pattern was termed 'processed/snacking'. The third pattern, 'African/Caribbean' was characterised by yam/cassava/plantain, red meat, chicken and turkey, soups (including African and Caribbean soups) and rice/pasta, fish and offal and was low in cheese, yoghurts and spreads.

Table 5:2**:** Maternal demographics of the analysed sample (n=482)

Maternal demographics		Mean (SD)/Median (IQR)/N (%)
Pre-pregnancy		
Age (years)		31.2 (5.2)
Ethnicity	*White*	329 (68)
	Black	110 (23)
	Asian	20 (4)
	Other	23 (5)
Years in full time education		15.0 (2.8)
Maternal BMI (kg/m^2) [a]		34.7 (32.5 to 37.9)
Nulliparous		229 (50)
Index of Multiple Deprivation Quintiles [b]	*1 (least deprived)*	30 (6)
	2	31 (6)
	3	55 (12)
	4	172 (36)
	5 (most deprived)	191 (40)
Maternal antenatal and neonatal demographics		
Mother assigned to UPBEAT Intervention		234 (49)
Gestational diabetes mellitus [c]		116 (25)
Birthweight (g)		3499 (499)
Large for gestational age >90th centile [d]		61 (12)
Small for gestational age <10th centile [d]		34 (7)

[a] Median (interquartile range); [b] Scores were calculated for the region of residence, by fifths of the population. UK-wide scores were developed from English and Scottish data relating to employment and income domains; [c] Gestational diabetes diagnosed using the International Association of Diabetes in Pregnancy Group's criteria at 24–28 weeks' gestation, [d] World Health Organisation (2007) z-score.

Table 5:3: Offspring demographics for the analysed samples (n=482)

Child 3-year follow-up demographics		
Age (years)		3.5 (0.28)
Female		243 (50)
Mother living with a partner		387 (80)
Mother a current smoker		47 (9)
Mode of infant feeding at 4 months	*Breastfed*	135 (52)
	Formula fed	105 (41)
	Mixed fed	18 (7)
BMI z-score [d]	472	0.88 (1.0)
Height-for-age z-score [d]	477	0.38 (1.1)
Weight-for-age z-score [d]	477	0.83 (1.0)
Weight-for-height z-score [d]	472	0.90 (1.0)
International Obesity Task Force gender specific cut-offs BMI categorises [e]	*Underweight (< 18.5 kg/m^2)*	15 (3)
	Healthy (18.5-24.9 kg/m^2)	292 (62)
	Overweight (25.0-29.9 kg/m^2)	125 (26)
	Obese (30.0-34.9 kg/m^2)	14 (3)
	Morbidly obese (≥35.0 kg/m^2)	26 (6)
Sum of skinfolds (mm) [a, f]	371	41.3 (34.0 to 50)
Percentage body fat (%)	382	22.3 (6.5)
Arm circumference (cm)	462	17.7 (1.8)
Waist circumference (cm)	466	53.0 (4.3)
Nutrient intake per day		
Energy (kcal)	481	954 (260)
Protein (% Energy)	481	16.3 (1.9)
Total Fat (% Energy)	481	34.1 (3.1)
Saturated Fat (% Energy)	481	15.4 (1.8)
Carbohydrate (% Energy)	481	53.2 (3.9)
Fibre (g)	481	8.7 (2.8)
Total Sugars (g/day)	481	65.5 (20)

[e] IOTF International cut-off as BMI references [f] sum of triceps, biceps, subscapular, suprailiac and abdominal skinfold thicknesses (mm). [d] World Health Organisation (2007) z-score.

Table 5:4: Adjusted associations between offspring dietary patterns at age 3-years and body composition

		Healthy		Processed and Snacking		African and Caribbean	
		Coefficient/ Odds ratio[+] (95% CI)		Coefficient/ Odds ratio[+] (95% CI)		Coefficient/ Odds ratio[+] (95% CI)	
BMI z-score [a, d]	472	-0.01 (-0.12 to 0.09)	p=0.82	0.06 (-0.04 to 0.16)	p=0.23	-0.08 (-0.21 to 0.04)	p=0.20
Body fat percentage (%)	382	-0.10 (-0.92 to 0.71)	p=0.80	0.66 (-0.10 to 1.43)	p=0.09	-0.64 (-1.41 to 0.48)	p=0.33
Height-for-age z-score [a, d]	477	0.02 (-0.08 to 0.13)	p=0.65	0.02 (-0.08 to 0.12)	p=0.69	0.07 (-0.05 to 0.21)	P=0.24
Height-for-weight z-score [a, d]	472	-0.02 (-0.12 to 0.08)	p=0.72	0.08 (-0.01 to 0.18)	p=0.09	-0.08 (-0.21 to 0.04)	p=0.18
Weight-for-age z-score [a, d]	477	-0.01 (-0.12 to 0.09)	p=0.75	0.05 (-0.04 to 0.15)	p=0.28	-0.007 (-0.13 to 0.12)	p=0.91
Arm (cm)	462	-0.1 (-0.29 to 0.08)	p=0.28	0.15 (-0.03 to 0.33)	p=0.10	-0.23 (-0.45 to -0.01)	P=0.04
Waist (cm)	466	0.06 (-0.39 to 0.51)	p=0.79	0.10 (-0.33 to 0.52)	p=0.66	-0.45 (-0.98 to 0.08)	P=0.09
Sum of skinfolds (mm) [b]	371	-1.76 (-3.30 to -0.14)	p=0.03	0.63 (-1.59 to 2.86)	p=0.57	-0.89 (-3.12 to 1.33)	p=0.43
Obese (IOFT cut off) [c, d]	472	1.07 (0.73 to 1.56)	p=0.70	1.53 (1.07 to 2.19)	p=0.002	0.61 (0.37 to 1.01)	p=0.056

Abbreviations: IOTF: International Obesity Task Force, gender specific BMI cut-offs; [a] Z-scores calculated using the WHO growth standards (2007); [b] sum of triceps, biceps, subscapular, suprailiac and abdominal skinfold thicknesses (mm); [c] Odds ratio. [+] Adjusted for maternal ethnicity, socio-economic status, smoking and BMI at baseline (15-18 weeks' gestation), years spent in full time education, maternal age, parity, infant birthweight, age at follow-up and sex and randomisation arm. [d] was not adjusted for infant sex or age at follow-up. Children were excluded if they were born ≤ 34 weeks gestation or suffering from major ill health.

Table 5:5: Adjusted association between offspring BMI category at 3-years of age and the Children's Eating Behaviour Questionnaire

	Underweight		Overweight		Obese	
	Coefficient (95% CI)					
Food approach scales	(n=15)		(n=125)		(n=38)	
Food responsiveness	-0.25 (-0.68 to 0.18)	p=0.25	0.27 (0.09 to 0.44)	p=0.003	0.47 (0.19 to 0.74)	p=0.001
Emotional overeating	-0.21 (-0.47 to 0.03)	p=0.096	0.05 (-0.04 to 0.15)	p=0.29	0.07 (-0.09 to 0.23)	p=0.39
Enjoyment of food	-0.62 (-1.09 to -0.16)	p=0.008	0.20 (0.02 to 0.399)	p=0.02	0.34 (0.05 to 0.64)	p=0.02
Desire to drink	0.20 (-0.40 to 0.81)	p=0.508	0.10 (-0.14 to 0.35)	p=0.41	0.42 (0.03 to 0.83)	p=0.03
Food avoidance scales						
Emotional under eating	0.008 (-0.49 to 0.50)	p=0.94	-0.07 (-0.27 to 0.13)	p=0.48	-0.20 (-0.52 to 0.11)	p=0.213
Slowness in eating	0.46 (0.005 to 0.93)	p=0.047	-0.08 (-0.27 to 0.09)	p=0.36	-0.40 (-0.70 to -0.11)	p=0.007
Food fussiness	0.71 (0.22 to 1.21)	p=0.005	0.02 (-0.18 to 0.22)	p=0.83	-0.28 (-0.60 to 0.03)	p=0.08
Satiety responsiveness	0.19 (-0.20 to 0.58)	p=0.34	-0.21 (-0.37 to -0.05)	p=0.009	-0.461 (-0.71 to -0.20)	p<0.001

Abbreviation: Adjusted for maternal ethnicity, socio-economic status, smoking and BMI at baseline (15-18 weeks' gestation), years spent in full time education, maternal age, parity, infant birthweight, sex age at follow-up and randomisation arm. Children were excluded if they were born ≤ 34 weeks gestation and suffering from major ill health.

Table 5:6 : Association between offspring dietary patterns at 3-years of age and maternal social and demographic factors (n=482)

	Healthy pattern		Processed and Snacking pattern		African and Caribbean pattern	
	Coefficient/ Odds ratio (95% CI)					
Maternal BMI (kg/m^2)	0.19 (-0.30 to 0.68)	p=0.44	0.02 (-0.42 to 0.47)	p=0.91	0.30 (-0.18 to 0.78)	p=0.23
Years in full time education (years)	0.41 (0.12 to 0.70)	p=0.005	-0.56 (-0.82 to -0.30)	p<0.001	-0.17 (-0.46 to 0.10)	p=0.22
Maternal age (years)	0.63 (0.09 to 1.17)	p=0.02	-0.63 (-1.12 to -0.14)	p=0.012	-0.19 (-0.72 to 0.34)	p=0.48
White vs black [a]	1.11 (0.86 to 1.43)	p=0.41	1.46 (1.14 to 1.86)	p=0.002	0.13 (0.09 to 0.21)	p<0.001
IMD Quintile	-0.1 (-0.22 to 0.01)	P=0.07	-0.01 (-0.12 to 0.09)	P=0.79	0.23 (0.11 to 0.35)	p<0.001

Abbreviations: BMI: Body mass index, IMD: Index of Multiple Deprivation. [a] Odds ratio; BMI, maternal age and years in full time education recorded at 15-18 weeks gestation. IMD quintiles are calculated for the region of residence, by fifths of the population. UK wide-scores were developed by reconciling Scottish data to English norms. Children were excluded if they were born ≤ 34 weeks gestation or suffering from major ill health.

Table 5:7: Descriptive statistics for the whole sample and stratified by gender for the subscales of the Children's Eating Behaviour Questionnaire

	All (n=507)	Female (n=259)	Male (n=248)
	Mean (SD)	Mean (SD)	Mean (SD)
Food responsiveness	2.12 (0.84)	2.12 (0.85)	2.12 (0.82)
Emotional overeating	1.41 (1.41)	1.38 (0.47)	1.43 (0.52)
Emotional under eating	2.68 (0.96)	2.62 (0.93)	2.73 (0.98)
Slowness in eating	3.13 (0.86)	3.14 (0.87)	3.13 (0.85)
Enjoyment of food	3.57 (0.90)	3.60 (0.89)	3.53 (0.91)
Desire to drink	2.79 (1.20)	2.73 (1.17)	2.85 (1.24)
Food fussiness	2.91 (0.94)	2.84 (0.95)	2.99 (0.94)
Satiety responsiveness	3.12 (0.75)	3.13 (0.79)	3.10 (0.71)

Abbreviations: SD: Standard deviations

Table 5:8: Unadjusted analysis of child eating behaviour at 3-years of age stratified by mode of early feeding in offspring born to obese women

	Breastfeeding n=140	Formula feeding n=111	Mixed feeding n=20	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Food responsiveness	2.18 (0.84)	2.04 (0.76)	2.12 (0.86)	0.39
Emotional overeating	1.44 (0.54)	1.42 (0.47)	1.3 (0.35)	0.53
Emotional undereating	2.78 (0.93)	2.63 (1.04)	2.86 (0.81)	0.39
Slowness in eating	3.00 (0.86)	3.14 (0.92)	3.19 (0.83)	0.26
Enjoyment of food	3.65 (0.84)	3.59 (0.86)	3.63 (0.90)	0.82
Desire to drink	2.62 (1.10)	2.70 (1.27)	2.2 (1.13)	0.22
Food fussiness	2.96 (0.90)	2.92 (1.06)	2.88 (0.89)	0.91
Satiety responsiveness	3.08 (0.70)	3.11 (0.77)	3.26 (0.66)	0.60

Abbreviations: SD: Standard deviations

5.4.2 Maternal demographics

In an unadjusted analysis (model 1) different maternal social and demographic characteristics were associated with the three childhood dietary patterns. A higher number of years in full time education and a higher maternal age were associated with the child having a higher score on a healthy/prudent dietary pattern. Fewer years in full time education, lower maternal age and having a White mother were associated with the child having a higher score on a processed/snacking dietary pattern. Having a Black mother and a greater deprivation defined by index of multi-deprivation were associated with the child having a high score on an African/Caribbean dietary pattern (Table 5:**6**, all $p<0.05$).

5.4.3 Dietary patterns and anthropometric measures and body fat percentage

In the adjusted regression model (model 2), the healthy/prudent dietary pattern was associated with a -1.76cm (95% confidence interval -3.30 to -0.14, $p=0.03$) lower sum of skinfolds. The processed/snacking pattern was associated with a higher odds of obesity [(BMI ≥30kg/m^2), defined using the IOTF gender-specific cut-odds (Cole and Lobstein, 2012)] (OR =1.53 (1.07 to 2.19) $p=0.04$). The African/Caribbean pattern was associated with a lower arm circumference (-0.23cm (-0.45 to -0.01), $p=0.04$, Table 5:***4***). No other dietary pattern-body composition associations were found.

Table 5:9: Factor loadings (≥±0.1) of items in the three dietary patterns identified

	Factor 1	Factor 2	Factor 3
1. White bread	-0.207	**0.3813**	
2. Brown bread	**0.3278**		-0.1675
3. Crisps and savoury snacks	0.11	**0.3782**	
4. Low sugar cereals	**0.264**	-0.1016	-0.1776
5. Medium & high sugar cereals	-0.2023	0.2123	0.1104
6. Boiled and baked potatoes	**0.352**	0.2178	-0.1422
7. Fried and roasted potatoes		**0.5194**	0.1203
8. Rice and pasta	**0.271**		**0.348**
9. Chicken and turkey	0.217	**0.2482**	**0.4132**
10. Red meat	**0.2351**	**0.2457**	**0.4761**
11. Offal			**0.2915**
12. Processed meat		**0.4992**	
13. Fish	**0.4234**		**0.3178**
14. Quiche and Pizza	0.146	**0.3099**	
15. Vegetarian dishes/food	0.1706		
16. Eggs	0.1864	0.1312	0.1219
17. Yam, cassava, plantain			**0.5508**
18. Vegetables	**0.6854**		0.1698
19. Root vegetables	**0.6555**		
20. Beans and pulses	**0.375**	0.1225	
21. Cooked and tinned fruit	**0.2346**	0.1656	0.16
22. Fresh fruit	**0.2803**		0.1188
23. Dried fruit	**0.2572**		
24. Nuts	**0.2321**		0.1005
25. Cheese and cottage cheese	0.1859	0.1494	**-0.2553**
26. Soup	0.1381		**0.4044**
27. Sauces and salad dressing	**0.3233**	0.1161	
28. Yoghurt		**0.2568**	**-0.2256**
29. Desserts and puddings		**0.4421**	0.1775
30. Cakes and biscuits		**0.4484**	0.1066
31. Confectionary	-0.1073	**0.5544**	
32. Spreads	**0.2335**	**0.3233**	**-0.2722**
33. Sweet spreads	0.2096	0.1746	
34. Hot drinks			
35. Milky drinks			-0.1132
36. Low sugar soft drinks		**0.2842**	-0.2094
37. High sugar soft drinks		**0.2426**	
38. Fruit juice	0.1462	0.1337	
39. Water		-0.1578	**0.2546**

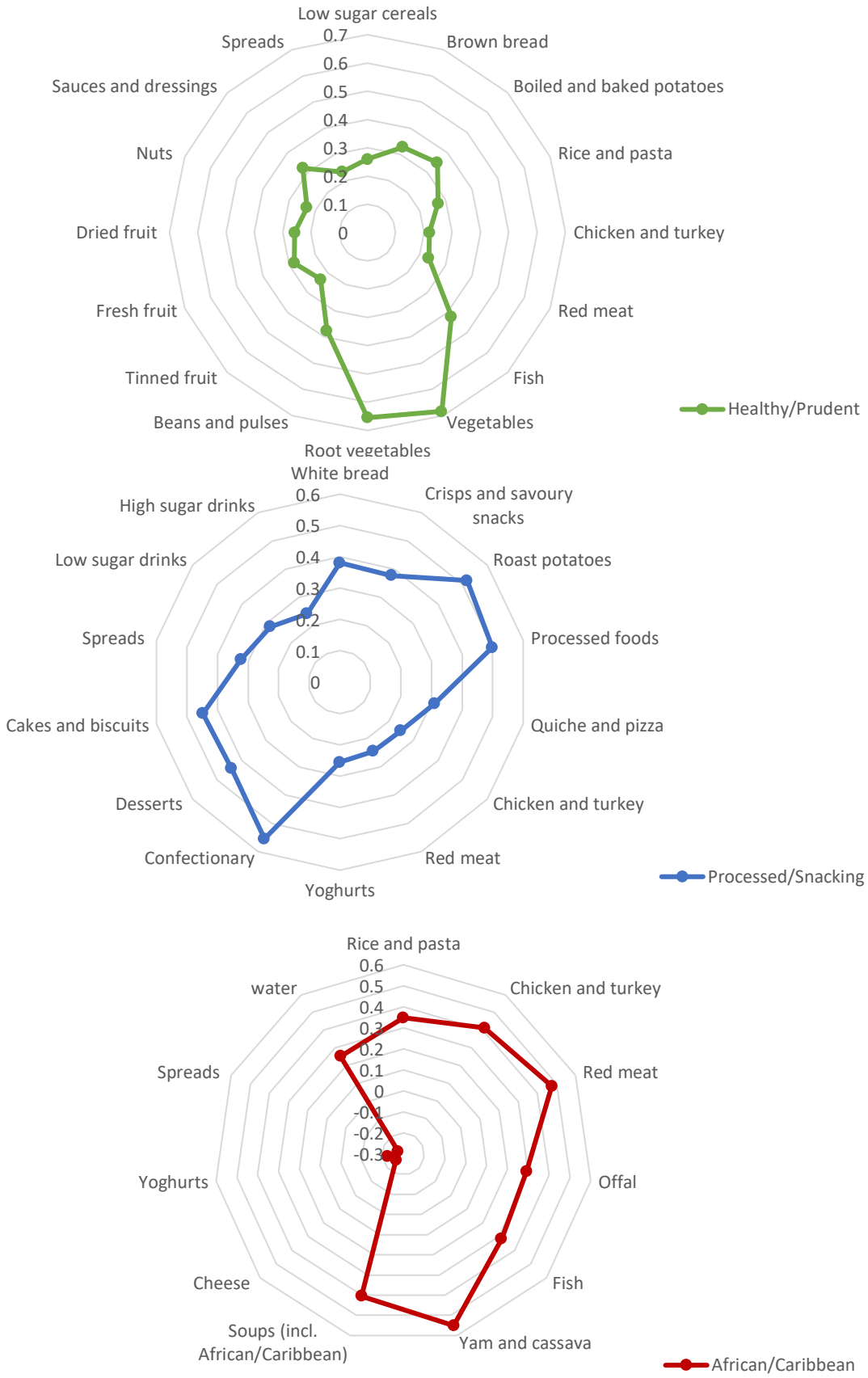


Figure 5:2: Radar graphs with factor loadings ≥ ±0.22 for each identified dietary pattern

5.4.4 Eating behaviour and body composition

There were no differences in the CEBQ scores according to gender or mode of infant feeding (Table 5:8 & Table 5:*9*). For the food approach scales, following adjustment for confounders, lower enjoyment of food and food responsiveness were associated with lower arm and waist circumferences, weight-for-age, weight-for-height and BMI z-scores and obesity (all $p<0.006$, Figure 5:4, Table 5:4). For the food avoidance scales, greater slowness in eating and satiety responsiveness were associated with a lower BMI z-score, a lower odds of obesity, weight-for-age, weight-for-height and height-for-age z-scores and arm and waist circumferences (all $p<0.009$, Figure 5:4, Table 5:4).Food fussiness was associated with a lower BMI, odds of obesity and weight-for-height z-score (all $p<0.002$, Figure 5:4, Table 5:4).

Emotional under eating was not associated with any measures of body composition or adiposity; emotional overeating was only associated with weight-for-height z-score ($p=0.02$). Body fat percentage and sum of skinfolds were not associated with any of the eating behaviour sub scales (data not shown). Grouping the children by BMI class, an obese BMI (IOTF BMI centile cut-off equivalent to ≥30kg/m^2) vs healthy, after adjustment for confounders, the children with obesity showed higher food approach scales scores for food responsiveness ($p=0.001$), enjoyment of food ($p=0.02$) and desire to drink ($p=0.03$). In contrast, the food avoidance scale, slowness in eating, and satiety responsiveness ($p<0.008$) were inversely associated with obesity (Table 5:**5** & Figure 5:5).

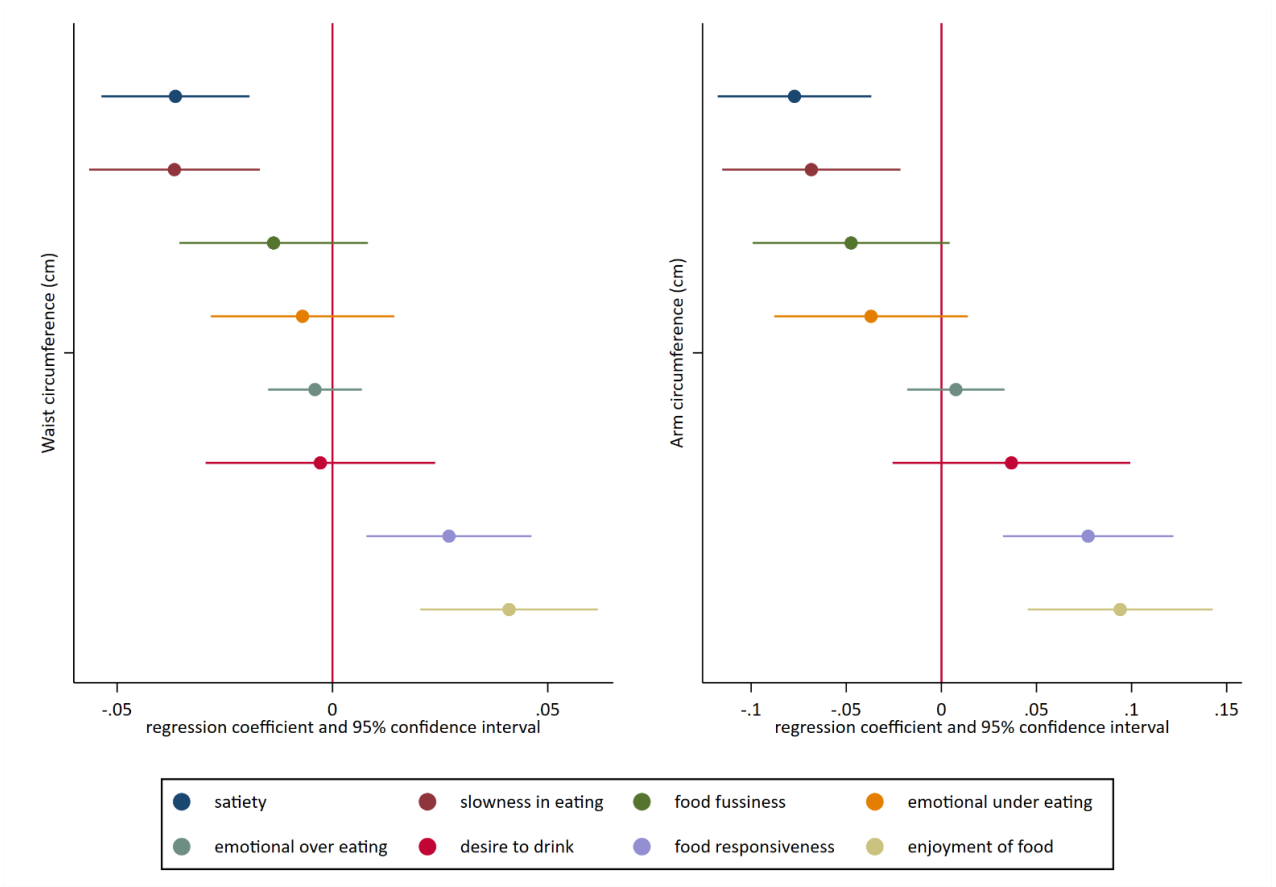


Figure 5:3: Associations between measures of the CEBQ and waist and arm circumferences in children at 3-years of age

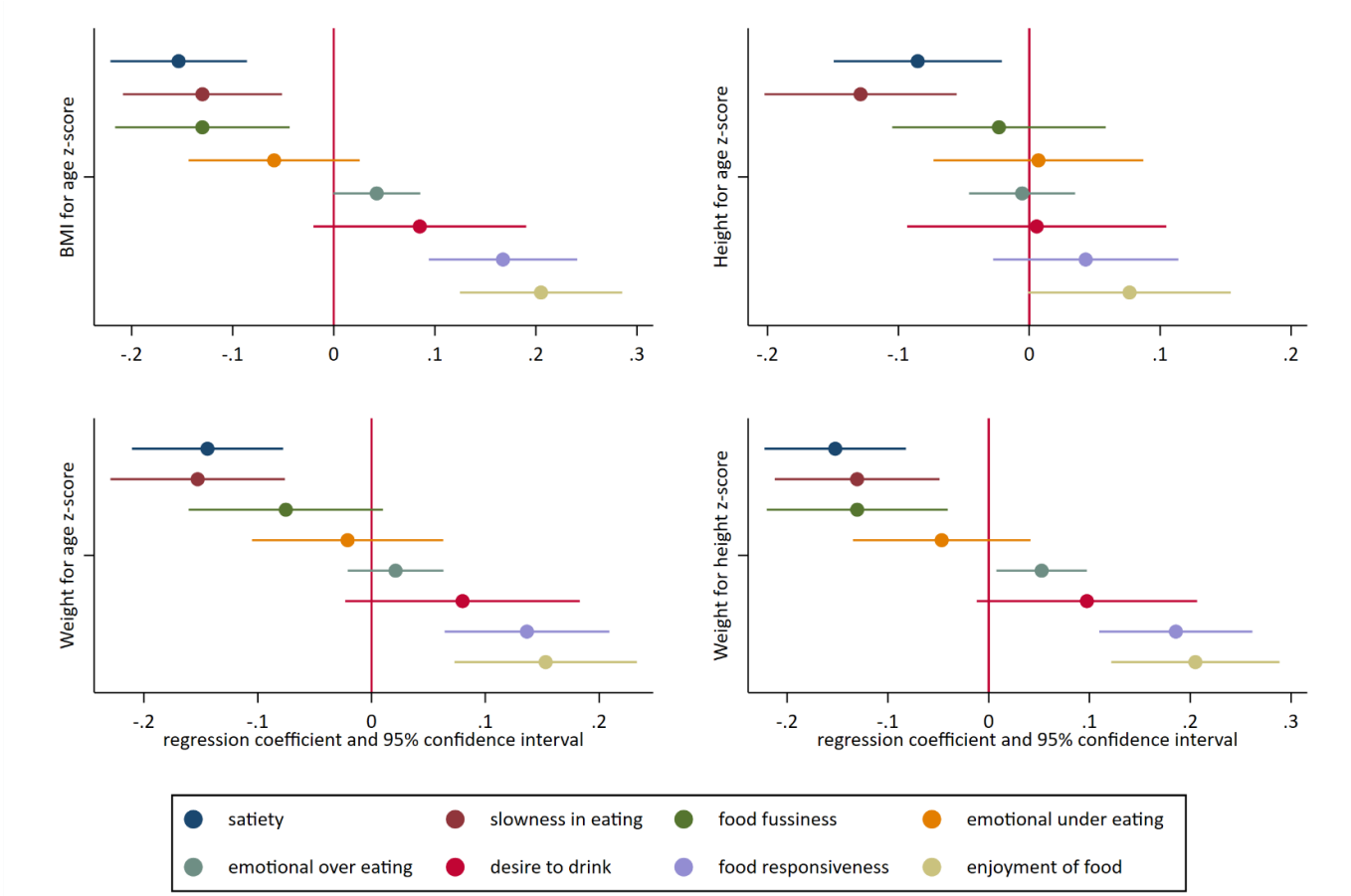


Figure 5:4:Associations between measures of the CEBQ and the WHO z-scores in children at 3-years of age

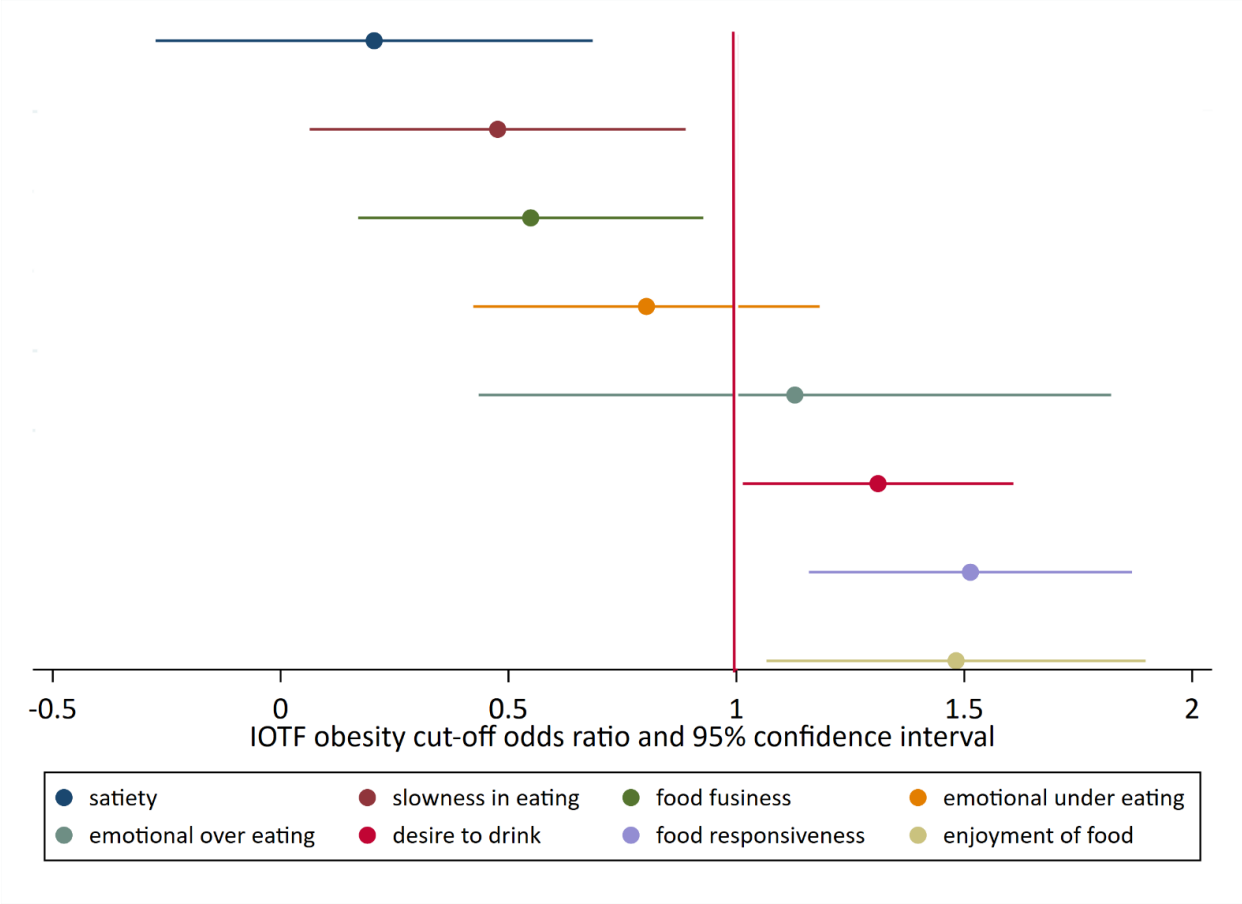


Figure:5:5:Associations between measures of the CEBQ and odds of childhood obesity at 3-years of age

5.5 Discussion

This study uniquely explores associations between dietary patterns and eating behaviours with BMI and measures of adiposity in 3-year-old children born to mothers with obesity from high social deprivation and ethnically diverse backgrounds.

Children with obesity had higher scores on a processed/snacking dietary pattern defined as a diet high in confectionary, crisps, processed foods, cakes and biscuits and greater food approach and less food avoidance eating behaviours. Dietary intake and body composition analyses in children have hitherto focused on specific food groups, such as sugar-sweetened beverages (Scharf and DeBoer, 2016), high sugar/fat snacks (Rollins et al., 2014) or fruit and vegetable intake (Kepper et al., 2016). However, dietary patterns reduce dietary data into fewer variables by combining highly correlated food groups, therefore they may better define an individual's habitual diet as they attempt to describe the whole diet rather than description of specific nutrients or foods (Hu, 2002). Whilst several studies have addressed relationships between dietary patterns and obesity in older children (Ambrosini, 2014), we are unaware of previous reports addressing dietary patterns and adiposity in three-year olds even though at this age the children may already be on a trajectory to development of later life obesity (Ward et al., 2017). Arguably, prevention at this age through appropriate dietary intervention may have particular gain in terms of prevention of adult obesity, as previous studies have reported that dietary patterns track from early childhood to later life (Mikkilä et al., 2005). A report of dietary patterns in the UK ALSPAC cohort of children described 'healthy', 'traditional' and 'processed' dietary patterns in children at 3-years of age (North and Emmett, 2000), whilst the healthy and processed patterns are similar to the present study, other differences may reflect ethnic diversity of the UPBEAT cohort. Comparison in relations to body composition is not possible as the ALSPAC study did not include measurement of adiposity, although there was no association between dietary patterns at 3-years and body mass index when measured at age 7-years (Reilly et al., 2005).

Our findings support those from the CHASE cohort who described that UK Black/African 9-10-year-old children benefit from maintaining a traditional African/Caribbean diet. This was evident from the observed association of high scores on an African/Caribbean dietary pattern with a lower arm circumference despite the Black women having a higher index of multi-deprivation. CHASE showed that a traditional African/Caribbean diet in late childhood was associated with an improved lipid profile, and compared to a White-European diet the

overall nutrient content was lower in total fats and higher in carbohydrates (Donin et al., 2010), and lower in processed foods, which might explain the relationship with the lower measure of adiposity.

We have previously reported the maternal dietary patterns of 1023 women obtained during the UPBEAT study (Flynn et al., 2016b) in which four distinct patterns were identified, “snacks”, “processed”, “fruit and veg” and “African/Caribbean”. Whilst only three patterns were identified in this analysis of the diets of their children they were broadly similar to those of their mothers three years previously, highlighting commonality of diet within families, as reported previously in the UK Southampton Women’s Survey (Fisk et al., 2011).

Similarly to dietary patterns, eating behaviours developed in early life track through childhood (Ashcroft et al., 2008). The validated CEBQ questionnaire has greatly facilitated studies of relationships between appetite traits and body composition (Wardle et al., 2001; Birch et al., 2007; Sleddens et al., 2008). Using this questionnaire, food responsiveness and enjoyment of food were associated with higher arm and waist circumferences, weight-for-age, weight-for-height and BMI z-scores and higher odds of obesity. In contrast slowness in eating and satiety responsiveness were inversely associated with the same measures of body composition, suggesting that these traits are protective against an obesogenic environment. Importantly, slower eating is a modifiable eating style which may reduce excessive weight gain in childhood. The associations between enjoyment of food and food responsiveness and increased body composition and rates of obesity, are consistent with previous studies suggesting that children with overweight or obesity are more responsive to food cues (Jansen et al., 2003; Webber et al., 2009; Boswell et al., 2018), but amongst these the only report of children at a similar age to this study was from an Australian cohort of 2-5 year old children, although the results were based on parent reported measurements (Boswell et al., 2018).

In agreement with BASELINE, an prospective maternal-child cohort study in 1189 2-year old children from Ireland (McCarthy et al., 2015) we did not find associations between emotional under/over eating and desire to drink and measures of body composition. This could be because the children were too young to display emotion in relation to eating habits. Although, in older children a similar lack of an association has been found. (Viana et al., 2008) This may imply that these three measures from the CEBQ do not have a major impact on body composition and adiposity compared to the other sub-scales.

The offspring of mothers with obesity are particularly at risk of obesity and this is the first study to address dietary patterns and eating behaviours associated with obesity in such children. As previously described by ourselves (Dalrymple et al., 2019a) and others, there is a striking relationship between maternal obesity and offspring risk of obesity (Catalano et al., 2009; Heslehurst et al., 2019). Whether this arises from shared familial environment, shared genes or the maternal *in utero* environment or a combination of all three is not established. Animal models and some of the human cohort studies however have argued for a major contribution of *in utero* determinants through persistent effects on the developing fetus, including modification of the pathways of energy balance at the level of the hypothalamus (Taylor and Poston, 2007; Molle et al., 2016). This is supported by the recent finding of an association between perinatal methylation of the SLC6A4 gene implicated in appetite regulation and obesity in later childhood (Lillycrop et al., 2019). Whether the relationships between food approach and food avoidance variables with measures of childhood adiposity in these children are a direct result of the *in utero* environment cannot be established from this study, although future comparisons of the strength of these relationships within cohorts of children from mothers of a healthy BMI, with appropriate adjustment for confounders, could shed light on the aetiology of these relationships.

5.5.1 *Strengths and limitations*

Strengths of the study include the rich UPBEAT dataset which provides comprehensive information on the eating habits and behavioural origins of early childhood obesity and multiple determinants of childhood body composition and adiposity. The sample of the mothers and their offspring included are ethnically diverse and of low socio-economic status. To our knowledge this the only study which has combined dietary patterns and eating behaviours in the same study of childhood obesity at any age. Limitations include loss to follow-up of the study population which may result in selection bias; however, there were no differences in the maternal population who completed the 3-year follow-up compared to those who did not, except for a higher proportion of white women returning for the 3-year visit. The CEBQ is a parent reported measure and is subject to recall bias and the main care giver's own interpretation of eating behaviours, however the CEBQ is validated and previous trials have reported high internal validity. The dietary patterns, derived using factor analysis, involve several arbitrary decisions including consolidation of food items into groups, the number of factors to extract, rotation method and naming of the factors. FFQs are also

associated with recall bias from the child's main caregiver (Martínez et al., 1998). The measures of body composition utilised in this study have limitations. BMI standardised cut-offs, z-scores, BIA and sum of skinfolds which was used to define obesity and adiposity in the children are indirect measures of fat mass; future studies should consider validating measures of body composition with DXA, which is widely recognised as a good measure of adiposity (Eisenmann et al., 2004). Lastly, our study was observational, so causality of the associations cannot be assumed.

In summary, we found that food approach eating behaviours and a diet high in processed and snacking foods were associated with obesity and measures of body composition at 3-years of age in children of mothers with obesity. Conversely slower eating, a "healthy/prudent" or a traditional "African/Caribbean" diet were associated with lower rates of obesity or adiposity. This study provides evidence for potentially modifiable determinants and adds credence to the view that promoting healthy food alternatives and eating behaviours should be considered for assimilation into public health strategies in high-risk children at risk of obesity in early life.

Chapter 6 : Modifiable early life exposures associated with cardiometabolic outcomes in 3-year old children born to mothers with obesity

6.1 Abstract

Background: Children born to mothers with obesity are at enhanced risk of obesity. This may result from in-utero exposures, genetic predisposition or shared family environment. Effective intervention strategies are needed to prevent obesity in these high-risk children; this requires evaluation of modifiable pregnancy and early-life risk factors.

Objectives: To assess the individual and cumulative effect of maternal and early-life modifiable exposures on childhood adiposity and obesity outcomes in 3-year-old children born to women with obesity.

Methods: The UPBEAT study, an antenatal lifestyle intervention in women with a BMI≥30kg/m2, has previously been associated with lower adiposity and resting pulse rate in the offspring at 6-months and 3 years-of-age, respectively. By analysing the UPBEAT study as a cohort, including adjustment for randomisation arm and appropriate confounders, we used regression analyses to assess the effect of modifiable exposures on measures of adiposity and obesity in 3-year-old children. Exposures included early pregnancy BMI, gestational weight gain, mode of neonatal feeding and childhood eating habits (assessed by the Childhood Eat Behaviour Questionnaire and factor analysis of a food frequency questionnaire). Childhood outcomes included skinfold thicknesses, body fat percentage, arm and waist circumferences, WHO z-scores and overweight/obesity (BMI≥25.0kg/m^2).

Results: 495 mother-child dyads participated. The UPBEAT intervention did not influence outcome variables. The exposures combined incrementally to increase childhood adiposity and obesity. For each additional exposure, children had a higher BMI z-score (b-coefficient: 0.35SD (95% confidence interval: 0.23 to 0.47)), arm circumference (0.59cm (0.40 to 0.79)) and overweight/obesity (OR 1.95 (1.46 to 2.59)). Compared to no exposures, children with four or more exposures had a higher BMI z-score (1.11SD (0.65 to 1.58)), arm circumference (2.15cm (1.41 to 2.89)) and overweight/obesity (6.52 (2.30 to 18.41)) (all $p<0.001$).

Conclusion: This study suggests that complex interventions which begin preconceptionally and continue pregnancy and early childhood, and target the exposures described in this study, offer a strategy for prevention of pre-school obesity.

6.2 Introduction

In parallel with the global obesity epidemic, childhood obesity is increasing worldwide (Di Cesare et al., 2019). Between 2000 and 2013 the number of overweight and obese children rose from 32 to 42 million (World Health Organisation, 2014), with global prevalence expected to reach 70 million by 2025 (World Health Organisation, 2016). The immediate effects of childhood obesity include health complications, such as behavioural disorders, fatty liver disease and asthma (Di Genova et al., 2018; Temple et al., 2016). Childhood or early-life obesity is known to track across the lifecourse (Ward et al., 2017) increasing the risk of cardiovascular disease (Hao et al., 2018) and type 2 diabetes (Abbasi et al., 2017) in the longer term. Prevention of childhood obesity is a worldwide public health priority (World Health Organisation, 2016).

In the UK a quarter of children enter primary school overweight or obese (NHS, 2015), with the highest prevalence amongst ethnic minorities and those living in disadvantaged areas (Public Health England, 2020). Amongst the potential environmental, genetic and lifestyle factors responsible, a substantial body of evidence implicates early life factors in the development of childhood obesity. Experimental animal studies (Menting et al., 2019), observational cohorts (Heslehurst et al., 2019) and some randomised controlled trials (Dalrymple et al., 2018) suggest that adverse in-utero exposures, including maternal obesity (Dalrymple et al., 2019a) or excessive gestational weight gain (GWG) (Voerman et al., 2019), may contribute to offspring obesity, which can persist into later life (Koletzko et al., 2012). Nutritional exposures in infancy and early childhood are also increasingly considered to be influential in development of childhood obesity (Fogel et al., 2020). These include, short or no breastfeeding duration (Harder et al., 2005; Breij et al., 2017), and the development of eating habits and behaviours, such as responsiveness to food (McCarthy et al., 2015), high intake of energy dense foods and a higher rate of food consumption (Fogel et al., 2017). Longitudinal analyses suggest that once established, these eating habits and behaviours persist into adulthood (van Jaarsveld et al., 2014). Therefore, effective strategies implemented during these windows of vulnerability are needed to stem the rising trend of childhood obesity.

To date, research on early-life determinants of childhood obesity has focused on children born to women of heterogeneous BMI (Gillman et al., 2008; Robinson et al., 2015), yet children of women with obesity are those at greatest risk. In accord with the World Health Organisation (WHO) ECHO report (World Health Organisation, 2016) recommending that

effective public health strategies to prevent childhood obesity be tailored to high-risk women and their families, we aimed to identify modifiable risk factors in a cohort confined to children of born to women with obesity (BMI≥30kg/m^2) of ethnic diversity and high social deprivation. In a follow-up study of the UK Pregnancies Better Eating and Activity Trial (UPBEAT) (Poston et al., 2015) we examined the effect of six modifiable early-life exposures and their cumulative effect on fourteen measures of offspring adiposity and obesity outcomes at 3 years of age. These exposures included early pregnancy BMI, GWG, mode of infant feeding and dietary intake and eating behaviours (food responsiveness and slowness in eating).

6.3 Methods

6.3.1 Setting

UPBEAT, a multi-centre randomised controlled trial, investigated the effect of an intense 8-week diet and physical activity intervention in 1555 pregnant women with obesity (BMI≥30kg/m^2) (Poston et al., 2015). Participants were randomised to the intervention or to standard antenatal care and were from UK inner-city settings of ethnic diversity and from high socioeconomically deprived backgrounds. Details of the intervention inclusion and exclusion criteria have been published previously (Briley et al., 2014). Research Ethics Committee approval was obtained in all participating centres, UK Integrated Research Application System; reference 09/H0802/5 (South East London Research Ethics Committee). All participants provided written informed consent. The intervention had no effect on the primary outcomes; the incidence of maternal gestational diabetes and large-for-gestational-age infants. However, there were improvements in some secondary maternal outcomes, including a reduction in total GWG (Poston et al., 2015).

6.3.2 3-year post-delivery follow-up

Between August 2014 and October 2017 participants in the UPBEAT study were invited to attend a 3-year post-delivery visit with their children. Of the 1555 women originally recruited, 514 mother-children dyads took part in the 3-year visit (Figure 6:1). The study design and protocol were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 13/LO/1108). The children were included in this analysis if they had 1) attended the follow-up visit at 3-years of age and 2) had body composition variables recorded during the 3-year visit. Children were excluded if they were suffering from severe illness (n=4) or if born before 34 weeks' gestation (n=5).

6.3.3 Exposures variables

For the purpose of this study we addressed relationships between maternal and early life (nutritional) exposures and measures of childhood adiposity and obesity. The maternal exposures were selected based on previous literature and were defined as: 1) early pregnancy BMI (30.0–34.9kg/m^2 vs ≥35.0kg/m^2; WHO classification, I vs II and III, (World Health Organisation, 2020)) measured at trial baseline (15^{+0}-18^{+6} weeks' gestation). Height

and weight were used to calculate BMI (kg/m^2); height was measured to the nearest 0.1cm with a portable stadiometer (Harpenden; CMS Weighing Equipment Ltd.). Weight was measured to the nearest 0.1kg with calibrated electronic scales (Seca), after removal of shoes and heavy clothing or jewellery; 2) GWG categorised using the National Academy of Medicine (NAM) guidelines (Institute of Medicine, 2009) (inadequate: <5kg vs adequate: 5-9kg vs excessive >9kg). GWG was calculated using estimated weight before pregnancy by the difference in the mother's weight measured at baseline minus 1.25kg and weight recorded at 34^{+0}-36^{+6} weeks gestation and 3) mode of infant feeding recorded on hospital discharge as exclusively breastfeeding, exclusively formula feeding or partial breastfeeding (defined as any breast feeding). The nutritional exposures were recorded at 3-years of age and included 4) a 'processed/snacking' dietary pattern score, 5) child's food responsiveness and 6) slowness in eating. The data collection and methodology of these dietary variables has been published previously (Dalrymple et al., 2019b). In brief, dietary patterns were derived using factor analysis of a culturally appropriate 85-item food frequency questionnaire. Eating behaviours were assessed using the validated Childhood Eating Behaviour Questionnaire (CEBQ) (Wardle et al., 2001), which consists of 35 items, divided into 8 eating behaviours. Two behaviours, slowness in eating and food responsiveness, were selected for analysis; as being most amenable to intervention (Scaglioni et al., 2018), Furthermore, we reported strong associations between these two eating behaviours and adiposity and obesity in the 3-year old UPBEAT children (Dalrymple et al., 2019b).

6.3.4 Child variables

6.3.4.1 Body composition and measures of obesity

Body composition was assessed by triceps, biceps, suprailiac, subscapular and abdominal skinfold thicknesses using children's Holtain skinfold callipers, sum of skinfold thicknesses (calculated by addition of the five measures), mid-upper arm and waist circumferences and body fat percentage assessed by ImpediMed Imp SFB7 bioelectrical impedance analysis (BIA). Weight to the nearest 0.1kg (using calibrated scales) and height (using the Leicester height measurer) to the nearest 0.1cm were used to derive the WHO z-scores (de Onis, 2006) and to define childhood overweight by International Obesity Task Force (IOTF) sex-specific centiles (boys overweight = 90.5th centile and girls overweight = 89.3th centile) (Cole and Lobstein, 2012).

6.3.5 Statistical analysis

As there was no effect of the UPBEAT intervention on the outcomes of interest, the data was treated as a cohort. Demographic results were expressed as mean ± standard deviation (SD), median and interquartile range or percent and number as appropriate. Children's sum of skinfolds was positively skewed and log-transformed for analysis. Depending on the outcome of interest, adjusted linear or logistic regression was used. All outcomes were adjusted for maternal age, parity, ethnicity, smoking status at baseline, years spent in full time education, randomisation arm and gestational age at delivery. Additional adjustments were made for child age at follow-up (months) and infant sex when indicated. Using regression analyses, we first reported the relationship between the individual maternal exposures (early pregnancy BMI, GWG and mode of infant feeding on hospital discharge) and measures of childhood adiposity and obesity outcomes. The second objective was to assess the incremental impact of the exposure variables on childhood outcomes, using three composite models were created: 1) maternal exposures (BMI, GWG and mode of feeding on hospital discharge), 2) nutritional exposures (processed/snacking dietary pattern score, food responsiveness and slowness in eating) and 3) the combined effect of all six exposures. To create the composite models, binary variables were derived for each exposure (BMI: 30.0–34.9kg/m^2=0, ≥35.0kg/m^2=1; inadequate/adequate GWG=0, excessive GWG=1 and exclusively breastfeeding=0, partial breastfeeding or formula feeding=1). As the dietary exposures are continuous variables, with no published reference guidelines to dichotomise the variables, we categorised a high (=1) association as mean ±1 SD, with the remainder categorised as normal/low (=0). Food responsiveness and the dietary pattern scores are positively associated with measures of adiposity, therefore the high categories were defined as mean + 1 SD, as slowness in eating in negatively associated with measures of adiposity the high category was defined as mean – 1 SD. Each child was assigned a score for the three models, the maternal model ranged from 0-3, the nutritional model ranged from 0-2, as categorises 2 and 3 were combined. For the combined model and overall score was calculated ranging from 0 to 6 (0 was the reference group for all models). Using adjusted regression, the association with childhood outcomes were examined on a continuous and categorical scale. All data was analysed using Stata software, version 15.0 (StataCorp, College Station, Texas).

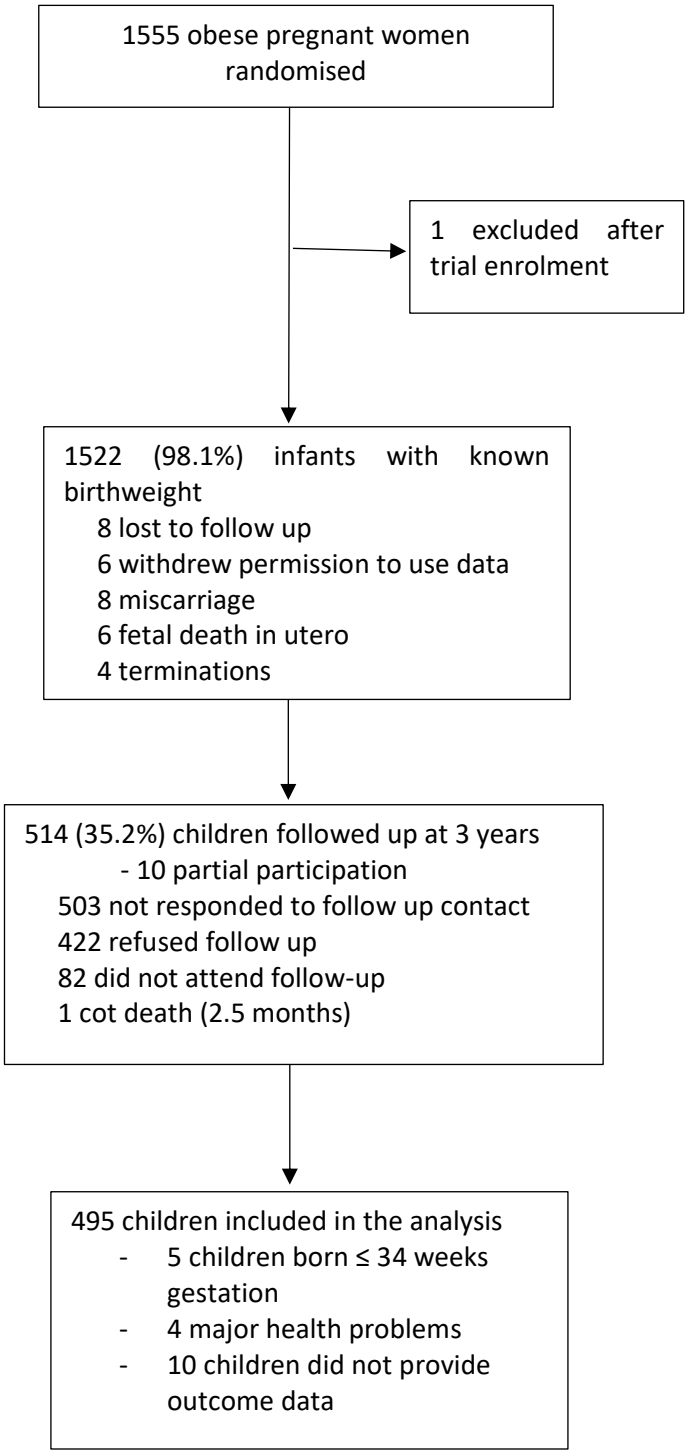


Figure 6:1: Consort diagram of participants enrolled in the UPBEAT trial at 3-years after delivery

Table 6:1: Maternal and demographics of the analysed sample (n=495)

Maternal demographics		Mean (SD)/ Median
Pre-pregnancy		(IQR)/N (%)
Age (years)		31.2 (5.3)
Ethnicity	White	337 (68)
	Black	114 (23)
	Asian	20 (4)
	Other	24 (5)
Years in full time education		15.1 (2.8)
Maternal BMI (kg/m^2)		34.7 (32.6 to 37.9)
Obesity class I (30.0-34.9 kg/m^2)[a]		266 (53.7)
Obesity class II (35.0-39.9 kg/m^2)[a]		143 (28.9)
Obesity class III (≥40.0 kg/m^2)[a]		86 (17)
Nulliparous		244 (49)
Index of Multiple Deprivation Quintiles	1 (least deprived)	28 (6)
	2	36 (7)
	3	56 (11)
	4	176 (35)
	5 (most deprived)	196 (40)
Maternal antenatal and neonatal demographics		
Mother assigned to UPBEAT intervention		241 (49)
Gestational diabetes mellitus		120 (26)
Gestational weight gain (kg)		7.5 (4.3)
Birthweight (g)		3499 (497)
Large for gestational age >90th centile [b]		62 (12)
Small for gestational age <10th centile [b]		35 (7)
Child 3-year follow-up demographics		
Age (years)		3.5 (0.28)
Female		244 (49)
Mode of infant feeding at hospital	Breastfed	312 (63)
discharge	Formula fed	96 (19)
	Mixed fed	86 (18)
World Health Organisation z-scores [c]		
BMI-for-age (n=485)		0.88 (1.0)
Height-for-age (n=490)		0.38 (1.1)
Weight-for-age (n=490)		0.83 (1.0)
Weight-for-height (n=485)		0.90 (1.0)
International Obesity Task Force BMI categorises [d]		
Underweight	< 18.5 kg/m^2	15 (3)
Healthy	18.5-24.9 kg/m^2	292 (62)
Overweight	25.0-29.9 kg/m^2	126 (27)
Obese	30.0-34.9 kg/m^2	14 (3)
Morbidly obese	≥35.0 kg/m^2	26 (5)
Measures of adiposity		
Sum of skinfolds (mm) (n=381)		41.3 (33.9 to 50.0)
Percentage body fat (%) (n=382)		22.4 (6.6)
Arm circumference (cm) (n=470)		17.8 (1.8)
Waist circumference (cm) (n=479)		53.3 (4.2)

Abbreviations: BMI: body mass index; cm: centimetre; g: grams; IQR: Interquartile range mm: millimetre; SD (Standard deviation; %: percent. [a] WHO BMI categories for adults. [b] Customised birthweight centile calculated by adjusting for maternal height, weight, ethnic origin, parity and infant sex; [c]Z-scores calculated using WHO Anthro (de Onis, 2006). [d] IOTF International gender specific cut-off as BMI references.

Table 6:2: Description and reasoning behind potential confounders

Confounder	Definition	Reasoning
Maternal age	Continuous	Increasing maternal age at childbirth is associated with a more favourable phenotype (taller stature and reduced abdominal fat) in their children (Savage et al., 2013)
Parity	Binary; 0-Nultip (reference), 1-Multip	Multiparty is independently associated with increasing infant adiposity (Gaillard et al., 2014b).
Maternal ethnicity	Categorical; 0-White (reference), 1-Black, 2-Asian, 3-Other	Differences in body composition in European and Asian populations has been reported from early infancy to adulthood (Stanfield et al., 2012).
Maternal educational attainment	Continuous; total years	Observational studies have identified a dose response relationship between educational attainment and childhood obesity (Lamerz et al., 2005)
Smoking status at baseline	Categorical; never smoked (reference) current smoker, ex- gave up before pregnancy, ex gave up in pregnancy	Maternal smoking status has been associated with increased adiposity in the offspring. (Robinson et al., 2015)
Gestational age at delivery	Continuous: gestational age in days	Due to the known association with body composition and gestational age.
Child sex	Categorical; Male, Female	There are known sex differences between boys and girls for measures of body composition in early childhood, including fat mass, percentage body fat and bone-free lean tissue mass (Taylor et al., 1997; Kirchengast, 2010).
Child age at follow-up	Continuous; age in months	The age of the UPBEAT children was 3.0 years to 4.0 years (mean = 3.5 years), this age is defined as a period of rapid growth and development (de Onis, 2006; Giles et al., 2015) and adjustment was made to account for differences in body composition across this age range.
Child physical activity level	Continuous; total minutes per week	Child's physical activity levels has been linked higher rates of obesity (Strong et al., 2005; Hills et al., 2013).
Child processed/snacking diet score	Continuous; z-score	Child's dietary intake has been reported to be associated with body composition and overweight and obesity (Dalrymple et al., 2019b).

6.4 Results*:*

Five hundred and fourteen (33%) of the 1555 women from UPBEAT agreed to participate and attended the follow-up appointments 3 years after delivery. At the follow-up visit 5 children were born <34 weeks' gestation, 4 were suffering from major ill health and 10 provided no outcome data for this analysis. The study population therefore comprised of 495 children (Figure 6:1). The average age of the mothers at trial baseline was 31.2 years, 49% were nulliparous, 68% were White and the median early-pregnancy BMI was 34.7kg/m^2 (32.5 – 37.9). The average GWG was 7.5 (4.3) kg and using the NAM guidelines for GWG, 28%, 35% and 37% of women were categorised as having inadequate, adequate and excessive GWG, respectively. 63% of mothers were exclusively breast feeding on hospital discharge. For the children, the average age at follow-up was 42 (3.4) months, the BMI z-score was 0.88 (1.0) and 35% were classified as having overweight/obesity according to the IOTF criteria (Table 6:1).

6.4.1 Maternal Body Mass Index

When compared to obesity class I, maternal pre-pregnancy BMI≥35kg/m^2 was associated with higher child arm (0.56cm; 0.24 to 0.88, p<0.001) and waist circumferences (0.88cm; 0.13 to 1.64, p=0.02); BMI (0.34; 0.15 to 0.53); weight-for-age (0.33; 0.15 to 0.52) and weight-for-height (0.37; 0.20 to 0.55) z-scores (all p<0.001). Also, maternal BMI ≥35kg/m^2 was associated with a greater odds of child overweight/obesity (1.65; 1.11 to 2.44, p=0.01) (Table 6:3).

6.4.2 Gestational Weight Gain

Excessive GWG (>9kg) was associated with higher child BMI (0.24; 0.002 to 0.47, p=0.04), weight-for-age (0.25; 0.17 to 0.49, p=0.03) and height-for-age z-scores (0.28; 0.49 to 0.53, p=0.01) (Table 6:4).

6.4.3 Mode of Infant Feeding

Compared to exclusive breastfeeding, formula feeding on hospital discharge was associated with higher child subscapular skinfold thickness (0.98mm; 0.07 to 1.88, p=0.03), logged sum of skinfolds (0.29; 0.003 to 0.57, p=0.04), arm circumference, (0.51cm; 0.06 to 0.96, p=0.02), BMI z-score (0.35; 0.09 to 0.62, p=0.01), weight-for-height z-score (0.31; 0.05 to 0.57, p=0.01)

and odds of overweight/obesity (OR 2.01; 1.17 to 3.45, p=0.01). Compared to exclusively breastfeeding at hospital discharge there were no associations between partial breastfeeding and any childhood outcome (Table 6:5).

6.4.4 Combined effect of maternal exposures

A score, from zero to three, based on three maternal exposures was generated for each child. 23% of the children had no exposures, 41% had one exposure, 30% had two exposures and 6% had three (Table 6:6). Child BMI z-score, weight-for-height (WH) z-score, arm circumference and overweight/obesity were included in the combined model analyses as these were most frequently associated with maternal risk factors. On a continuous scale, for each additional maternal exposure, child WH and BMI z-scores increased by 0.25 SD (0.13 to 0.36, p<0.001) and 0.23 SD (0.12 to 0.36, p<0.001), respectively. For overweight/obesity, the odds ratio increased by 1.44 (1.12 to 1.86, p=0.004), and arm circumference by 0.35cm (0.16 to 0.55, p<0.001). Compared to children with no exposures, for those with three exposures WH and BMI z-scores increased by 0.78 (0.33 to 1.23) and 0.79 (0.31 to 1.27, p<0.0001), respectively (Table 6:6). Similarly, the odds of overweight/obese increased by 2.66 (1.01 to 7.00, p=0.04) and arm circumference by 1.04cm (0.25 to 1.82, p=0.01) (Table 6:6).

6.4.5 Combined effect of dietary exposures analysis

For the dietary exposures (range 0-3), categorises 2 and 3 were combined. 58% of children had no exposures, 31% had one exposure, 11% had two or more exposures (Table 6:7). On a continuous scale, for each additional dietary exposure children had an increase in WH and BMI z-scores of 0.28 SD (0.15 to 0.341 p<0.001) and 0.29 SD (0.15 to 0.43, p<0.001), respectively. For overweight/obesity, there was an increase in odds of 1.75 (1.31 to 2.33, p<0.001), and for arm circumference an increase of 0.44cm (0.21 to 0.68, p<0.001). Compared to children with no exposures, children with two or more exposures had an increase of 0.56 (0.27 to 0.86) and 0.60 (0.30 to 0.90) for WH and BMI z-scores (both p<0.001), respectively (Table 6:7). There was a 2.87 (1.54 to 5.37, p=0.001) increase in the odds for overweight/obesity and an increase of 0.90cm (0.38 to 1.43, p=0.001) in arm circumference

6.4.6 Combined effect of maternal and early life exposures

For the final model, the maternal and childhood dietary exposures were combined. The total score ranged from 0-5 (no child was assigned all 6 risk factors). The children were subdivided into groups with 0 exposures (15%), 1 exposure (29%) 2-3 exposures (49%) 4-5 exposures (7%), Table 6:8. Compared to children with no exposures, children with four or more had an increase in WH and BMI z-scores of 1.08 (0.64 to 1.51) and 1.11 (0.65 to 1.58) (both $p<0.0001$), respectively (Figure 6:2, Table 6:8). There was an increase in odds for overweight/obesity of 6.52 (2.30 to 18.41, $p<0.0001$) and in arm circumference of 2.15cm (1.41 to 2.89, $p=0.001$) (Figure 6:3, Table 6:8).

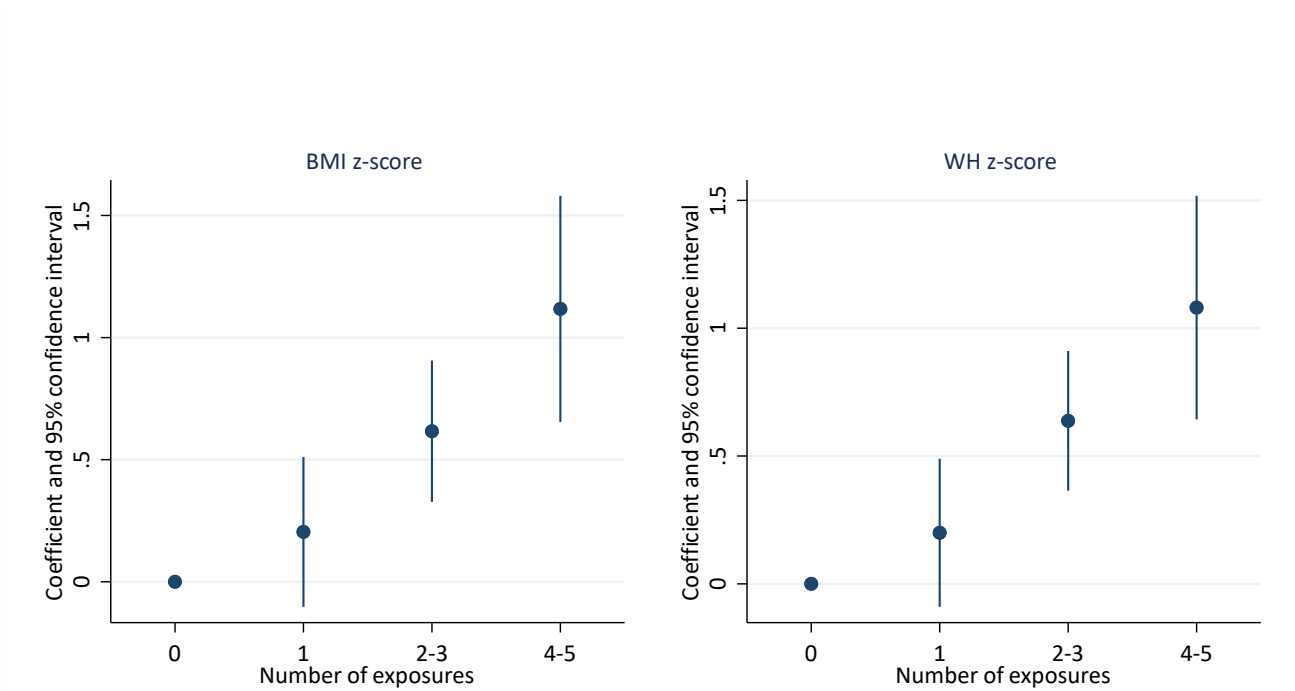


Figure 6:2: Adjusted coefficients for BMI z-score and WH z-score according to the number of exposures.

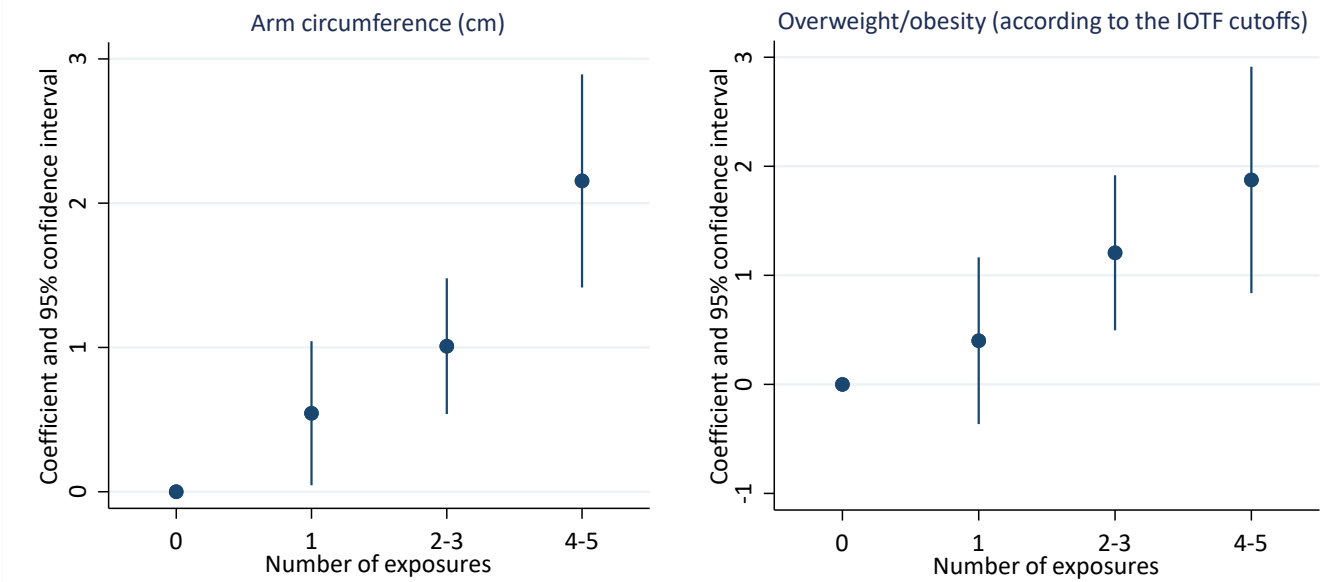


Figure 6:3: Adjusted coefficients for arm circumference and overweight/obesity according to the number of maternal exposures.

Table 6:3: Child adiposity and cardiometabolic outcomes according to maternal BMI

Child		**30.0-34.9kg/m²**		**≥35.0kg/m²**		
Skinfold thickness and adiposity	**N**	**Mean (SD)/Median (IQR)**	**N**	**Mean (SD)/Median (IQR)**	**Coefficient (95% CI)***	**p-value**
Subscapular (mm)	237	7.93 (3.2)	182	8.15 (3.3)	0.25 (-0.37 to 0.89)	0.42
Triceps (mm)	246	12.07 (3.9)	198	12.41 (4.0)	0.46 (-0.28 to 1.21)	0.22
Bicep (mm)	242	8.14 (3.6)	196	8.52 (3.4)	0.44 (-0.23 to 1.11)	0.19
Suprailiac (mm)	226	6.75 (3.7)	170	7.37 (3.8)	0.61 (-0.15 to 1.37)	0.11
Abdominal (mm)	227	9.23 (4.4)	180	9.88 (4.6)	0.66 (-0.21 to 1.54)	0.13
Sum of skinfolds (mm)	218	39.5 (32.6 - 48.3)	168	42.8 (36.7 - 50.9)	0.06 (0.003 to 0.13)∞	0.04
Total body fat (%)	207	21.8 (6.3)	175	23.1 (6.9)	1.16 (-0.17 to 2.50)	0.08
Circumferences						
Waist circumference (cm)	258	52.9 (4.0)	221	53.8 (4.4)	0.88 (0.13 to 1.64)	0.02
Arm circumference (cm)	254	17.5 (1.6)	216	18.0 (1.9)	0.57 (0.26 to 0.90)	<0.001
World Health Organisation z-scores [a]						
BMI	265	0.73 (0.9)	220	1.07 (1.1)	0.34 (0.15 to 0.52)	<0.001
Weight-for-age	266	0.68 (1.0)	224	1.00 (1.1)	0.33 (0.15 to 0.52)	<0.001
Weight-for-height	265	0.73 (0.96)	220	1.11 (1.0)	0.37 (0.20 to 0.55)	<0.001
Height-for-age	265	0.30 (1.12)	225	0.47 (1.0)	0.17 (-0.01 to 0.37)	0.07
International Obesity Task Force [b]						
(BMI≥25.0 kg/m²)	258	77 (29)	215	89 (41)	1.65 (1.11 to 2.44)	0.01

*Abbreviations: BMI: body mass index; CI: Confidence intervals; cm: centimetres; IQR: interquartile range; mm: millimetres; %: percentage. [a] Z-scores calculated using WHO Anthro, (de Onis, 2006). [b] IOTF International gender specific cut-off as BMI references. * Difference in mean adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery and child sex and age at follow up. Z-scores and IOTF categories were not adjusted for infant sex or age at follow-up. ∞ log transformed coefficients.*

Table 6:4: Child adiposity and cardiometabolic outcomes according to the National Academy of Medicine gestational weight gain guidelines

Child	Inadequate (<5kg)		Adequate (5-9kg)		Excessive (>9kg)	
	N	Mean (SD)/Median (IQR)	N	Mean (SD)/Median (IQR)	N	Mean (SD)/Median (IQR)
Skinfold thickness and adiposity						
Subscapular (mm)	111	8.1 (3.8)	130	7.6 (2.9)	134	8.1 (2.9)
Triceps (mm)	118	12.2 (4.0)	137	11.8 (3.9)	144	12.4 (3.6)
Biceps (mm)	117	8.5 (3.9)	136	8.04 (3.2)	140	8.3 (3.5)
Suprailiac (mm)	107	6.6 (4.1)	124	6.9 (3.7)	123	7.3 (3.4)
Abdominal (mm)	108	9.6 (4.3)	127	9.2 (4.3)	130	9.5 (4.7)
Sum of skinfolds (mm)	101	39.7 (33.5 – 51.3)	119	41.1 (33.4– 50.0)	121	42 (35.7 – 49.5)
Total body fat (%)	102	22.5 (6.4)	119	21.9 (6.7)	124	22.8 (7.0)
Circumferences						
Waist circumference (cm)	127	53.0 (4.3)	149	52.7 (4.2)	156	53.3 (4.2)
Arm circumference (cm)	126	17.6 (1.7)	144	17.6 (1.5)	155	17.9 (1.8)
World Health Organisation z-scores [b]						
BMI	127	0.83 (1.0)	151	0.79 (1.0)	159	1.00 (1.0) [¥]
Weight-for-age	128	0.64 (1.1)	152	0.79 (1.0)	161	0.96 (1.0) [¥]
Weight-for-height	127	0.81 (1.0)	150	0.83 (0.9)	159	1.01 (1.0)
Height-for-age	128	0.15 (1.2)	151	0.35 (1.0)	161	0.54 (1.0) [¥]
International Obesity Task Force [c]						
Overweight/obesity	124	43 (34)	146	46 (32)	154	63 (41)

*Abbreviations: BMI: body mass index; CI: confidence intervals; cm: centimetres; IQR: interquartile range; kg: kilograms; mm: millimetres; SD: standard deviation; %: percentage. [b] Z-scores calculated using WHO standards (de Onis , 2006). [c] IOTF International gender specific cut-off as BMI references. [¥] Significantly different. *Mean difference adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery and child sex and age at follow up. Z-scores and IOTF categories were not adjusted for infant sex or age at follow-up.*

Table 6:5: Child adiposity and cardiometabolic outcomes according to mode of infant feeding on hospital discharge

Child	Breastfeeding (n=315)	Formula feeding (n=98)		Partial breastfeeding (n=87)	
Skinfold thickness and adiposity		Mean difference/odds ratio (95% CI)*			
Subscapular (mm)	ref	0.98 (0.07 to 1.88)	0.03	0.35 (-0.51–to 1.22)	0.42
Triceps (mm)	ref	0.62 (-0.44 to 1.69)	0.25	-0.84 (-1.89 to 0.19)	0.11
Biceps (mm)	ref	0.56 (-0.38 to 1.52)	0.24	-0.25 (-1.19 to 0.68)	0.60
Suprailiac (mm)	ref	0.77 (-0.32 to 1.86)	0.16	-0.03 (-1.09 to 1.02)	0.94
Abdominal (mm)	ref	0.74 (-0.50 to 1.99)	0.24	-0.20 (-1.41 to 1.01)	0.74
Sum of skinfolds (mm)	ref	0.09 (0.01 to 0.18)∞	0.04	-0.01 (-0.10 to 0.07)∞	0.78
Total body fat (%)	ref	1.62 (-0.29 to 3.55)	0.09	0.44 (-1.38 to 2.27)	0.63
Circumferences					
Waist circumference (cm)	ref	0.78 (-0.29 to 1.87)	0.15	-0.65 (-1.68 to 0.39)	0.22
Arm circumference (cm)	ref	0.51 (0.06 to 0.96)	0.02	-0.20 (-0.65 to 0.24)	0.36
World Health Organisation z-scores [b]					
BMI	ref	0.35 (0.08 to 0.62)	0.01	-0.02 (-0.28 to 0.24)	0.87
Weight-for-age	ref	0.06 (-0.20 to 0.33)	0.63	-0.07 (-0.33 to 0.18)	0.59
Weight-for-height	ref	0.31 (0.05 to 0.57)	0.01	0.02 (-0.23 to 0.27)	0.86
Height-for-age	ref	-0.19 (-0.46 to 0.08)	0.17	-0.18 (-0.45 to 0.09)	0.20
International Obesity Task Force [c]					
Overweight/obesity	ref	2.01 (1.17 to 3.45)	0.01	0.91 (0.52 to 1.58)	0.74

*Abbreviations: BMI: body mass index; CI: Confidence intervals; cm: centimetres; IQR: interquartile range; mm: millimetres; SD: standard deviation; %: percentage. [b] Z-scores calculated using WHO standards (de Onis, 2006). [c] IOTF International gender specific cut-off as BMI references. *Mean difference adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery and child sex and age at follow up. Z-scores and IOTF categories were not adjusted for infant sex or age at follow-up. ∞ log transformed coefficients*

Table 6:6: Measures of childhood obesity according to number of maternal exposures

Number of exposures	Number (%)	WH Z-score [a] Coefficient (95% CI)	P-value*	BMI z-score [a] Coefficient (95% CI)	P-value*	Overweight/obesity (BMI ≥25kg/m²) [b] Odds ratio (95% CI)	P-value*	Arm circumference (cm) Coefficient (95% CI)	P-value*
0	101 (23)	ref		ref		ref		ref	
1	181 (41)	0.14 (-0.10 to 0.39)	0.25	0.14 (-0.12 to 0.40)	0.30	1.06 (0.60 to 1.89)	0.824	0.40 (-0.02 to 0.83)	0.06
2	135 (30)	0.45 (0.18 to 0.72)	0.001	0.41 (0.13 to 0.69)	0.004	1.94 (1.07 to 3.51)	0.029	0.74 (0.28 to 1.19)	0.002
3	26 (6)	0.78 (0.33 to 1.23)	0.001	0.79 (0.31 to 1.27)	0.001	2.66 (1.01 to 7.00)	0.046	1.04 (0.25 to 1.82)	0.01
Beta		0.25 (0.13 to 0.36)	<0.0001	0.23 (0.12 to 0.36)	<0.0001	1.44 (1.12 to 1.86)	0.004	0.35 (0.16 to 0.55)	<0.0001

*Abbreviations: BMI: body mass index; CI: confidence intervals; cm: centimetres. [a] Z-scores calculated using WHO Anthro (de Onis, 2006). [b] IOTF International gender specific cut-off as BMI references. * Difference in mean adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery, child sex, age at follow up, processed/snacking diet score and weekly physical activity. BMI Z-score and IOTF category were not adjusted for child sex or age at follow-up.*

Table 6:7: Measures of childhood obesity according to number of dietary exposures

Number of exposures	Number (%)	WH Z-score [a] Coefficient (95% CI)	P-value*	BMI z-score [a] Coefficient (95% CI)	P-value*	Overweight/obesity (BMI ≥25kg/m²) [b] Odds ratio (95% CI)	P-value*	Arm circumference (cm) Coefficient (95% CI)	P-value*
0	283 (58)	ref		ref		ref		ref	
1	149 (31)	0.29 (0.09 to 0.50)	0.004	0.27 (0.06 to 0.50)	0.01	1.91 (1.23 to 2.97)	0.004	0.43 (0.06 to 0.80)	0.021
2+	53 (11)	0.56 (0.27 to 0.86)	<0.001	0.60 (0.30 to 0.90)	<0.001	2.87 (1.54 to 5.37)	0.001	0.90 (0.38 to 1.43)	0.001
Beta		0.28 (0.15 to 0.41)	<0.001	0.29 (0.15 to 0.43)	<0.0001	1.75 (1.31 to 2.33)	<0.0001	0.44 (0.21 to 0.68)	<0.0001

*Abbreviations: BMI: body mass index; CI: confidence intervals; cm: centimetres. [a] Z-scores calculated using WHO Anthro (de Onis, 2006). [b] IOTF International gender specific cut-off as BMI references. * Difference in mean adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery, child sex and age at follow up. BMI Z-score and IOTF category were not adjusted for child sex or age at follow-up.*

Table 6:8: Measures of childhood obesity according to number of combined exposures

Number of exposures	Number (%)	WH Z-score [a] Coefficient (95% CI)	P-value*	BMI z-score [a] Coefficient (95% CI)	P-value*	Overweight/obesity (BMI ≥25kg/m²) [b] Coefficient (95% CI)	P-value*	Arm circumference (cm) Coefficient (95% CI)	P-value*
0	65 (15)	ref		ref		Ref		ref	
1	123 (29)	0.19 (-0.09 to 0.49)	0.17	0.20 (-0.10 to 0.51)	0.19	1.49 (0.70 to 3.20)	0.304	0.54 (0.04 to 1.04)	0.03
2-3	212 (49)	0.63 (0.36 to 0.91)	<0.001	0.61 (0.32 to 0.90)	<0.0001	3.34 (1.64 to 6.80)	0.001	1.00 (0.54 to 1.48)	<0.0001
4+	30 (7)	1.08 (0.64 to 1.51)	<0.0001	1.11 (0.65 to 1.58)	<0.0001	6.52 (2.30 to 18.41)	<0.0001	2.15 (1.41 to 2.89)	<0.0001
Beta		0.36 (0.24 to 0.47)	<0.0001	0.35 (0.23 to 0.47)	<0.0001	1.95 (1.46 to 2.59)	<0.0001	0.59 (0.40 to 0.79)	<0.0001

*Abbreviations: BMI: body mass index; CI: confidence intervals; cm: centimetres. [a] Z-scores calculated using WHO Anthro (de Onis, 2006). [b] IOTF International gender specific cut-off as BMI references. * Difference in mean adjusted for maternal age, parity, ethnicity, smoking status at baseline, years in full time education, randomisation arm, gestational age at delivery, child sex and age at follow up. BMI Z-score and IOTF category were not adjusted for child sex or age at follow-up.*

6.5 Discussion

This study reports several novel findings. First, we have demonstrated strong associations between maternal early-pregnancy BMI, GWG, and mode of infant feeding and measures of adiposity and obesity in 3-year old children born to mothers with obesity. Next, we found that eating behaviours and dietary intake in the children were related to obesity. These relationships were not explained by adjustment for confounders, and provide the first demonstration that these maternal exposures, previously implicated in children from weight heterogenous mothers (Robinson et al., 2015), are also applicable to children of obese mothers and likely to make an important contribution to their high risk of obesity. Uniquely, we observed positive, additive associations between each of these maternal and nutritional exposures and childhood adiposity and obesity suggesting that each of these modifiable factors is worthwhile target for intervention.

In agreement with a meta-analysis of children aged 1-18 years (Heslehurst et al., 2019), and our previous study in 6-year old children from the SCOPE cohort (Dalrymple et al., 2019a), we also found that maternal early-pregnancy BMI was strongly associated with childhood adiposity and obesity in 3-year olds. These associations have also been described in animal models of maternal obesity in which maternal metabolic disturbances have been implicated through persistent developmental changes in the fetus which predispose the offspring to obesity (Poston, 2012). Furthermore, in support for our findings, excessive maternal GWG has also been reported as a risk factor for offspring obesity (Hinkle et al., 2012; Gaillard et al., 2015). A recent meta-analysis of 37 cohorts, assessed the separate and combined association of maternal BMI and GWG with the risk of overweight/obesity throughout childhood, in common with our study the effect of pre-pregnancy BMI was a greater determinant of childhood overweight/obesity that GWG. Importantly, in this meta-analysis the greatest association of maternal BMI and GWG were observed in late childhood (10-18 years). Translation of the increasing strengths of these association with age suggests that as the UPBEAT children progress through childhood and adolescence, prevalence of overweight and obesity could substantially increase from the current rate of 35%.

Formula feeding on hospital discharge (within 72hrs of delivery) was independently associated with increased rates of obesity and adiposity compared to breastfed children. We have previously shown in this cohort that adiposity in 6-month infants was associated with

formula feeding (Patel et al., 2018) and we now report that in this cohort of children born to obese mothers, that this persists until early childhood. This concurs with previous studies in children of weight heterogenous women, including the CHOP RCT which attributed higher adiposity rates in formula-fed children compared to breast fed children to the higher protein content of formula milk (Koletzko et al., 2009). Our data also concords with the recent WHO European Childhood Obesity Surveillance Initiative from 22 European countries which concluded that formula feeding from birth was associated with the highest rates of obesity in older children (6-9 years) born to women of heterogeneous BMI (Rito et al., 2019). Whilst the benefits of any breastfeeding on prevention of childhood obesity remain equivocal (Woo Baidal et al., 2016; Yan et al., 2014) our findings support initiation of breastfeeding at birth to optimise early growth trajectories in pre-school children born to women with obesity. Importantly, we report for the first time that maternal BMI, GWG and neonatal feeding combine independently to increase the risk of childhood obesity in 3-year old children of obese mothers.

Several studies have previously reported independent relationships between eating behaviours (McCarthy et al., 2015) or dietary intake (Flynn et al., 2020; Okubo et al., 2015) and childhood body composition. To our knowledge no previous study has assessed the combined impact of these nutritional exposures on childhood outcomes. We have recently reported the associations between dietary patterns, eating behaviours and body composition and adiposity in 3 year old children from the same cohort (Dalrymple et al., 2019b). Here, analysing the exposures on a continuous scale, we found positive independent relationships between a high 'processed/snacking' dietary pattern, food responsiveness and childhood overweight/obesity. Conversely, we found a negative relationship between slowness in eating and childhood outcomes. This present study provides an extra level of detail by combining the impact of these eating habits and behaviours and confirms a robust association between these exposures and childhood adiposity and obesity.

Finally, evaluating the combined effect of all maternal and postnatal exposures on childhood outcomes, compared to children with no exposures, the odds of being overweight/obese was over 6-times higher for children with 4 or more exposures. Two previous mother-child cohorts, The Southampton Women's Survey (SWS) (Robinson et al., 2015) and Project Viva (Gillman et al., 2008) have similarly reported how maternal variables can summate to increase the risk of childhood obesity. Both cohorts combined GWG, smoking in pregnancy

and short breastfeeding duration in the risk factor model, with SWS also including maternal BMI and vitamin D status, and Project Viva adding reduced infant sleep as additional exposures. Although the exposures differ for these cohorts, together with the results presented here there is strong evidence for a cumulative effect of multiple risk factors on the development of childhood obesity. However, a limitation of these earlier studies was that women were recruited prior to the recent increase in prevalence of obesity and included women with a predominantly healthy BMI. Given that many observational studies illustrate that children of women with obesity are most at risk of developing obesity, this study adds to the literature by demonstrating cumulative risk of early-life exposures in this high-risk group. The importance of this observation lies in the translational potential for combined interventions from preconception to postpartum to reduce childhood obesity in children born to obese mothers.

6.5.1 Strengths and limitations

Strengths of the study include the rich UPBEAT dataset which provided comprehensive information including multiple indicators of childhood body composition, adiposity and cardiovascular function. The mother-child dyads were ethnically diverse and included those from a low socioeconomic backgrounds, a population which are at high-risk of obesity (UK Government: Department of Health and Social Care, 2018). To our knowledge, the UPBEAT cohort is unique in its' population of mothers with pre-pregnancy obesity, the size of the cohort and with detailed *in-utero*, early postnatal and dietary exposures and multiple health outcomes, with a focus on measures of childhood adiposity. This enabled adjustment for several important confounding factors. Moreover, very few studies have focused on children of this age, yet it is recognised that pre-school adiposity tracks into adulthood (Ward et al., 2017). The main limitation is the observational study design, which is subject to residual confounding and potential overestimation of reported effects. The measures of adiposity and obesity, although detailed, have some limitations. BMI is an indirect measure of fat mass, and the BIA method has not been validated against dual-energy x-ray absorptiometry, the gold standard for adiposity measurement (Eisenmann et al., 2004).

In conclusion, this study has identified several exposures in pregnancy and early childhood which are cumulatively associated with increased obesity in 3-year-old children born to mothers with obesity. To date, research focused on reducing childhood obesity has predominantly consisted of interventions focusing on a single age group with little

demonstrable benefit (i-WIP Collaborative Group, 2017; Narzisi and Simons, 2020). This study highlights the need for a complex intervention beginning pre-conceptionally and continuing postpartum in order to reduce pre-school obesity. These interventions should encompass pre-conceptual care, weight management in pregnancy, breastfeeding support as well as dietary advice for pre-schoolers. We await with interest the results of the HELTI cohort which uniquely adopted this approach (Draper et al., 2019).

Chapter 7 General discussion

7.1 General discussion

The objectives of this thesis were to assess in the context of a randomised controlled trial, the effect of an antenatal lifestyle intervention in women with obesity on offspring cardiometabolic outcomes at 3-years of age. The associations of in utero and early life exposures on these cardiometabolic outcomes were also explored. The women and their children included within this thesis were from ethnically diverse background and of high social deprivation. Therefore, these findings are uniquely placed to inform public health strategies for high-risk children which focus on the prevention of obesity. This chapter provides a general discussion of the main findings, as well general methodological strengths and weaknesses, future research considerations and suggestions for public health strategies.

7.2 Summary of findings

The first of the results chapter, the systematic review (chapter 3), highlighted that follow-up of antenatal interventions for weight management in pregnancy remains an emerging field with little strong evidence that childhood obesity can be influenced by the current management strategies. This systematic review included the UPBEAT 6-month analysis which showed a reduction in a measure of adiposity in children. Chapter four describes how this effect of the intervention was sustained at 3-years of age. However, for the first time, an antenatal intervention of diet and physical activity in women with obesity has been shown to reduce resting pulse rate in pre-school children and resulted in a sustained improvement in maternal dietary intake, 3-years after delivery.

The observational analyses in chapters 5 and 6 identified modifiable in utero exposures associated with adverse adiposity and obesity outcomes in the 3-year of children which include a high maternal BMI during pregnancy (either severely or morbidly obese) and excessive gestational weight in pregnancy. The postnatal exposures associated with adverse childhood adiposity and obesity included formula feeding from birth, and dietary habits at 3-years of age. These included a high intake of processed and snacking foods, high food responsiveness and enjoyment of food. Conversely, lower measures of adiposity were associated with a 'healthy/prudent' or a traditional 'African/Caribbean' dietary intake, slowness in eating and higher satiety. These outcomes will now be discussed in light of relevance to public health.

7.3 Lifestyle interventions in pregnancy and early childhood outcomes

Prior to completing the UPBEAT analyses, I sought to investigate, through a systematic review process, whether antenatal lifestyle interventions in pregnant women aimed at modifying diet and/or physical activity had led to a reduction in measures of offspring obesity in early childhood. The results were assessed in the context of the intervention design and by maternal pre-pregnancy BMI. Although numerous trials have been completed in the antenatal period (summarised in Appendix 1); this review only identified eight RCTs which have reported offspring outcomes from six months to seven years of age. The eight antenatal interventions used a combination of diet and/or physical activity approaches in the trial design. All trials including GWG as a primary (n=5) or secondary outcome (n=3), six reported a significantly lower GWG in the intervention arm. The primary findings of the childhood follow-up trials showed that there were no differences in infant or childhood outcomes amongst the RCTs including women of heterogenous BMI. However, two interventions in women with obesity, UPBEAT and Healthy MOMs, were associated with reduced measures of obesity in infants at 6 and 12 months of age, respectively. The overall findings were limited by the heterogeneity of methodology and variations in reported outcomes.

These findings suggest a potentially greater influence of the antenatal intervention in women with obesity, for whom antenatal dietary and physical activity changes may have a profound effect on metabolic adaptations and thus the in utero environment. The null findings for women with a 'healthy' or 'overweight' BMI category could imply that these women may already have a healthy lifestyle, and although the interventions were able to reduce GWG, the metabolic adaptations associated with normal pregnancy were unchanged. Of interest, in a separate UPBEAT analysis by Mills et al. (2019), the metabolic profile of women in the UPBEAT trial according to trial allocation has been reported (n=1158). The authors found a marked change in lipids and lipoproteins across pregnancy for women assigned to the lifestyle intervention. At the time of the 6-month follow-up study this data was not available although the cord metabolome showed no significant difference between the intervention arms which might imply that the fetal metabolic exposures at delivery are not responsible to persistent change in offspring phenotype and that any persistent influence arises from exposures earlier in pregnancy (Patel et al., 2017b). Further analysis is therefore warranted as the metabolic adaptations observed antenatally may have influenced the measures of adiposity reported in the infants at 6-months of age. This secondary analysis of the UPBEAT

trial would provide evidence of the in utero metabolic implications on infant adiposity born to women with obesity.

7.4 The effect of the UPBEAT intervention on childhood cardiometabolic outcomes

For the first time, I have addressed the effect of an antenatal lifestyle intervention in women with obesity on childhood cardiovascular and metabolic outcomes at 3-years of age. The assessment of cardiovascular function was prompted by models in experimental animals which have shown consistently an effect of maternal adiposity on offspring cardiovascular outcomes.

Whilst only ~33% childhood follow-up was achieved; this represents the largest cohort of pre-school children studied following a lifestyle intervention in pregnancy. Despite a trend towards lower values in several measures of body composition, including sum of skinfold and odds of overweight or obesity, there was no evidence to suggest that the antenatal intervention reduced adiposity in the offspring. Although there are many reports of the consequence of maternal obesity on offspring outcomes from experimental animals (Menting et al., 2019), as detailed in chapter 3 very few lifestyle interventions in women with obesity have addressed the influence of the intervention on childhood outcomes, other than our previous report in 6-month old infants (Patel et al., 2017a). Together with the study by Vesco et al. (2016) these observations would imply that any effect on offspring outcomes may diminish overtime. A drawback of all of these studies is the very modest effect, associated with an overarching lack of improvement in clinical outcomes. Therefore, from a clinical and life course perspective it is essential that interventions are developed which have a greater benefit for the health of the mother to adequately address the hypothesis raised.

The most appropriate age to study these children should also be considered, as the adiposity rebound which starts at the age of 4 may mask any effect of the intervention and therefore, by analysing the children at an older age there may be greater conformity with measures of adiposity. This is borne out by strong relationship between maternal BMI and offspring adiposity as I published in the 6-year-old children from the SCOPE cohort and with similar reports from other mother-child cohorts e.g SWS and Generation R (Gaillard et al., 2014a; Robinson et al., 2015).

I also reported in this chapter that the UPBEAT lifestyle intervention in pregnancy was associated with a reduction in resting pulse rate in the offspring at 3-years of age. I hypothesis that this could be associated with reduced GWG and improved diet and physical activity in the mother, mediated by persistent effects on fetal physiology. This is a particularly exciting finding in view of the robust animal studies which suggest persistent programming of the central autonomic nervous system and a recently published study (Husin et al., 2020) that even in utero the developing fetus in obese women demonstrates increased brain autonomic activity. Our department is now analysing an extensive investigation funded by the British Heart Foundation, which has investigated neonatal heart rate and heart rate variability in a sub-group of the UPBEAT cohort by state of the art magnetic resonance imaging (MRI) as well as a comparison of infants born to women with a normal BMI. This study has also completed a follow-up in UPBEAT 3-year olds in which cardiac function has been studied by ECHO ultrasound and heart rate variability by measurement of the echocardiogram. The MRI data in the neonates (n=33) has shown that infants born to mothers with a high BMI had an increased heart rate and decreased left ventricular diastolic volume, (this work will be presented at the Pediatric Academic Societies meeting May 2020). Furthermore, in a recent analysis of these 3-year old children, interesting differences in cardiac structure between the trial arms are evident (unpublished data). Ongoing investigation of the UPBEAT cohort in late childhood included detailed assessment of cardiovascular function and adiposity will provide further insight into the long-term effects of the antenatal intervention on childhood cardiometabolic outcomes. Others have shown that GDM is associated with a fetal heart rate during an OGTT in women with a GDM diagnosis, compared to those without (Fehlert et al., 2017). It remains to be determined whether glycaemia is a predominant determinant of persistent cardiovascular changes in the offspring of women with obesity.

Furthermore, the UPBEAT antenatal intervention was associated with sustained improvements in maternal dietary intake 3 years after delivery. Although there was no effect on maternal body composition, these dietary changes may influence longer-term metabolic health. These persistent improvements support the notion that due to increased healthcare professional contact during pregnancy it is therefore a window of opportunity to intervene and promote maternal and child health.

7.5 Early life exposures and childhood cardiometabolic outcomes

The final two chapters described the relationship between antenatal and early life exposures and adiposity and obesity outcomes in the 3-year old UPBEAT children. Remarkably, a review of the literature determined that very little research has focused to date on eating habits of children born to mothers with obesity. I first sought to describe the dietary patterns of pre-school born to women with obesity, and analysed the associations between dietary intake, eating behaviours and body composition at 3-years of age. This analysis demonstrated that in these high-risk children, those who follow a "processed/snacking" dietary intake, which included high consumption of crisps, chips, processed foods, cakes and biscuits, was associated with higher measures of obesity. Conversely, a "healthy/prudent" or a traditional "African/Caribbean" pattern were associated with lower measures of adiposity. These diets differed in a number of ways, but they were both high in fish, white meat and vegetables, and had low associations with high-sugar drinks and confectionary.

For the eating behaviours, food avoidance behaviours, including slowness in eating and high satiety were associated with lower measures of adiposity. On the contrary, food approach behaviours including food responsiveness and enjoyment of food were associated with higher measures of adiposity and obesity. Although may factors have been shown to influence dietary habits, including socio-demographic characteristics, media and the family environment, the importance of these findings lies in their translatability to public health strategies. Eating habits and behaviours are established in early life and have been shown to track through into adulthood, therefore by promoting healthy dietary advice and guidance of eating behaviours in the early years may alleviate the burden of obesity which is evident in pre-school children. Implementation in public health strategy in the UK will require recognition of this and other relevant studies; this can come through changes in guidelines for public health strategy and indeed through direct communication with public health England.

The final analysis reported on the relationships between maternal and early life exposures, associated with an obese pregnancy, and offspring adiposity and obesity outcomes. By examining the individual exposures on measures of offspring body composition, I was able to then combine the exposures and develop a risk factor model. The results present a striking picture of the potential impact maternal obesity and its associated exposures, can have on the development of obesity in the child. Important observations from this research highlight

that a BMI ≥35kg/m^2 and excessive GWG in pregnancy, formula feeding from birth as well as unhealthy dietary habits are all associated with a greater odds of obesity.. This work highlights the importance of intervening during the antenatal or early postnatal period to alleviate the effect these exposures have on offspring cardiometabolic outcomes. Furthermore, the results provide a rationale to promote lifestyle changes preconceptionally as to reduce BMI and to potential lower excessive GWG, these arguably need to be a public health focus in the months leading up to conception.

7.6 Methodological strengths and limitations

The strengths and limitations of individual studies included in this thesis have been described in each chapter. To summarise the strengths, the data presented in this thesis is from a prospective cohort of women with obesity, recruited from ethnically diverse backgrounds of high-social deprivation. The in-depth data collection through pregnancy and early life provides a unique database, including maternal demographic, clinical, familial and environmental characteristics as well as comprehensive anthropometric data which allows for detailed analyses into the associations and determinants of childhood obesity. Together, the UPBEAT and UPBEAT 3-year follow-up databases are one of the largest resources for women with obesity and their children, which provides a unique opportunity to address relationships from mother to child. Future follow-ups of the children before they reach adolescence are well placed due to the extensive data collection.

Limitations include attrition of the study population, which is a common occurrence of randomised controlled trials. Although the sample size was large enough to provide an appropriate comparison of data, attrition introduces bias to the results and although this can be explored by assessing the method for missing data and completing sensitivity analyses, replication of the results published in this thesis are required in other mother-child cohorts. Furthermore, the inclusion of a normal weight comparator group would be of interest, especially comparing body composition measures at 3-years of age. Another consideration is the observational study design utilised in Chapters five and six as causal inferences cannot be obtained from this type of study design. Importantly, the assessment of childhood body composition and cardiovascular included indirect methods which were not validated against the gold standard techniques. Future studies should consider accurate assessment of body fat distribution, such as DXA, and imaging of cardiovascular structure and function using magnetic resonance imaging.

Finally, three of the result chapters included data from self-reported questionnaires which are known to be at risk of information bias. During the UPBEAT data collection validated food frequency questionnaires were used to assess maternal and child dietary intake. FFQs are a retrospective dietary assessment method that can provide detailed nutritional composition data. They are designed to collect data on habitual intake and have low participant and researcher burden, allowing assessment of large sample sizes in an efficient manner. However, the effectiveness of FFQ data is limited by the number of food items included in the questionnaire and is reliant on participant recall and appropriate reporting. Although there is no ideal dietary assessment method, FFQs have been reported to have low accuracy when compared to other dietary assessment methodologies and FFQs require accurate evaluation when developing the questionnaire. Therefore, an understanding of the inherent limitations of this method is essential when interpreting the findings presented in the results chapters. Similarly, maternal physical activity and the child's eating behaviour were assessed by the IPAQ and CEBQ, respectively. Although these questionnaires have been validated in women and children of heterogenous BMI, when choosing a questionnaire in a research context it is important to use a tool that has been validated in a similar population to maintain the validity.

7.7 Further research on the UPBEAT trial

Throughout the process of this thesis I have identified a number further analyses which could be carried out on the UPBEAT dataset.

- As part of a collaboration with the University of Southampton the children's Buccal cell samples have been analysed and epigenetic changes associated with body composition will be analysed by May 2020. Further analyses are also planned which will explore associations between the cord metabolome and body composition at 6 months and 3-years of age.
- The blood spot samples of the children have been analyses for branch chain amino acids and lipid profiles. This will provide an opportunity to analysis the association between child's dietary intake and metabolic profile.
- Exploration of the maternal metabolic adaptations observed antenatally and their associations with reduced subscapular skinfold thickness reported in infants at 6-months of age.

- Using similar methodology used in chapter 6, it would be possible to identify antenatal and postnatal modifiable factors associated with successful postpartum weight loss in women who participated in UPBEAT.
- We are also currently in the process of contacting women from the UPBEAT trial to establish the interest in attending an 8 to 10-year post-delivery follow-up study for the women and their child. This will allow further understanding of the longer-term implications of the intervention and we plan to complete in-depth analysis using gold standard measures of body composition to ascertain the body composition of these children. To maximise on recruitment, we plan to arrange 'away-days' at the eight UPBEAT hospitals organised within the school holidays to encourage participation and data collection.

7.8 Future research considerations

A surprising observation for the children who returned at 3-years of age, was the 35% prevalence of overweight or obesity, using the IOFT criteria. This is a 40% increase on the current UK rate for overweight and obesity for pre-school children. This high rate of obesity in the UPBEAT cohort presents a challenge for public health and highlights the need for appropriate and timely interventions to reduce the prevalence of obesity in children who are already at high-risk and on a trajectory to remain obese into later life.

It is also imperative that antenatal lifestyles interventions include longer-term follow ups to truly ascertain if interventions in pregnancy are associated with improved offspring cardiometabolic outcomes. These follow-ups should include detailed assessment of body composition using the gold standard method; DXA and magnetic resonance imaging for detailed assessment of the cardiovascular function. Furthermore, it would be advantageous for future trials to report comparable offspring outcomes and separate findings by maternal BMI class. This would allow for results to be pooled in a meta-analysis, which would greatly increase statistical power and identify key maternal characteristics which contribute to child health outcomes.

There is incontrovertible evidence suggesting an association between maternal obesity and childhood outcomes, this may arise from in-utero exposures, genetic traits, or shared family environment. Given the evidence of the early origins of obesity, antenatal interventions focused on changing maternal diet and/or physical activity have consistently been

considered as a potential strategy for the prevention of childhood obesity. Over the past 2 decades this has led to a global research approach focused on this particular area. Pregnancy is considered to be a critical time point in which women are amenable to behaviour change, due to the important implications for her unborn children. However, as highlighted in chapter 3, the overall effect of these antenatal interventions confer limited benefits for mother and child. Common methodological approaches of these trials include initiation at the start of the second trimester and interventions which promote modest changes to diet and physical activity. Clearly, alternative approaches to the current strategy is urgently required to improve maternal and offspring outcomes.

An emerging body of evidence now suggests that maternal preconception and early pregnancy metabolic health programmes early placenta function. This can result in epigenetic modifications in fetal tissue which has been shown to play a mechanistic role in metabolic disease programming through the in-utero environment. These alterations to maternal/placental function occur during the first 12 weeks of pregnancy, prior to when most of these interventions have been initiated. Therefore, future research strategies, should comprise of interventions which commence in the preconception period and continue throughout pregnancy. Furthermore, the current research has been conducted in women from all BMI groups. Arguably, conducting interventions in women with a healthy BMI will have limited impact on maternal and offspring outcomes and does not justify the resources expended in achieving the proposed outcome. Therefore, it would be pragmatic for future funding opportunities to solely focus on women at high-risk. Therefore, these interventions can be tailored, and personalised interventions for women with obesity to ensure that these women and their children have the best outcomes.

Finally, a common concern within this research domain is the high rates of attrition across the study period. Retention of participants should be a key consideration for all future trials, potential strategies to mitigate this form of bias would be main consistent contact with study participants throughout the trial, using e-technology to engage participants and to explore new strategies to record data, such as using alternative locations to collect data (e.g. travelling to a participants home, using a roving van for data collection or setting up data collection points within schools or local community centres).

7.9 Conclusion

This thesis reports several novel findings of associations between in utero and early life exposures on childhood cardiometabolic outcomes up to 3-years of age.

- A systematic review of randomised controlled trials reported that measures of obesity up to 12 months of age have been shown to be reduced by antenatal lifestyle interventions in women with obesity.
- There is evidence to suggest that an antenatal lifestyle intervention, of diet and physical activity, improved offspring resting pulse rate at 3-years of age. The intervention was also shown to contribute to long-term improvements in maternal dietary intake, 3-years after delivery.
- The dietary patterns and eating behaviours of pre-school children, born to women with obesity have been described. Associations between a "processed/snacking" dietary pattern was associated with greater odds of childhood obesity. Conversely, slowness in eating and higher satiety responsiveness were associated with lower measures of adiposity and obesity.
- The combined effect of early life exposures (maternal early-pregnancy BMI, GWG, mode of infant feeding and eating habits and behaviours in early childhood) was associated with large differences in adiposity and odds of overweight and obesity at 3-years of age.

Obesity in pregnancy is arguably one of the biggest challenges for public health in the UK. Acutely, it has a significant impact on reproductive health, including infertility, complications in pregnancy and labour and in the longer-term is associated with development of type 2 diabetes and cardiovascular disease in the mother. It also plays a crucial role in the cardiometabolic health of the child. Given the concerning implication of the intergenerational cycle of obesity from mother to child, this thesis has identified that an antenatal lifestyle intervention in women with obesity has the potential to improve cardiovascular outcomes in pre-school children and can result in a sustained improvement in maternal dietary intake 3-years after delivery. This work has also identified modifiable maternal exposures which are associated with higher adiposity and obesity prevalence in the child. These identified exposures have the potential to be focus of public health strategies which aim to reduce childhood obesity and cardiovascular dysfunction. This thesis provides support that pregnancy is an opportunity to educate women on positive health changes,

which have the potential to prevent adverse health outcomes for the child and improve dietary intake in the mother.

Appendices

Appendix 1: Summary of published and registered trials of antenatal interventions which include an offspring follow-up

Author, year, clinical trial number and trial name	Country	Design	Population	Maternal BMI (kg/m²)	Intervention	Offspring follow-up age	Follow-up rate	Outcome	Result
	Published trials								
Mustila et al. (2012)	Finland	Quasi-RCT	105	All	Individual counselling on PA and diet at 5 routine visits. Option to attend supervised group PA sessions.	0-48 months	66%	Postnatal weight development	No effect
Horan et al. (2014) ROLO Study	Ireland	RCT	781	All	1 group dietary session before <18 weeks'. Introduced to the rationale of low GI diet and provided with written resources for swapping to low GI foods.	6 months	35%	Body composition	No effect
Rauh et al. (2015) FeLIPO study	Germany	Cluster-RCT	250	All	Two individual counselling sessions, including nutrition PA and GWG monitoring and personalised feedback on their 7-day food and activity diaries	0-12 months	88%	Weight	No effect
Tanvig et al. (2015) LiP Study	Denmark	RCT	304	>29.9	Four individual dietary counselling sessions with a dietitian to provide a personalised diet. Encouraged to be physically active for 30-60 minutes daily.	2.5-3.2 years	52%	Body composition	No effect
Kolu et al. (2016) NELLI Study	Finland	Cluster-RCT	399	All	Counselling sessions designed to increase PA and to adhere to Finnish dietary recommendations regarding	7 years	43%	BMI	No effect

					the intake of fats, sugar, fibre, fruit and vegetables.				
Vesco et al. (2016) Healthy Moms Trial	USA	RCT	114	>29.9	Individual and group dietary and PA counselling sessions. Daily food and activity diaries were recommended and reviewed weekly.	12 months	78%	Body composition	Reduction in weight-for-age z-scores
Poston et al. (2015) UPBEAT	UK	RCT	1555	>29.9	Health trainer-led group & individual sessions over 8 weeks. Women received advice on strategies used to achieve goals, provided with booklets with recommended foods, recipes and suggestions for PA (DVDs of exercise regimen, a pedometer, and a log book for recording their weekly goals).	4-8 months	46%	Body composition	Lower SCSF thickness and z-score
Ronnberg et al. (2017)	Sweden	RCT	374	All	Education about IOM guidelines for recommended GWG according to BMI category. Personalised graphs including recommended interval of GWG.	5 years	80%	BMI	No effect
	Expected completion date								
Herring et al. NCT02229708	USA	RCT	262	25.0-44.9	A technology-based healthy lifestyle program for African-American mothers to improve their eating and activity during pregnancy	0-12 months		Change in infant weight and length	March 2018 – baseline data available
Roberts et al. NCT01643356	USA	RCT	50	25-40	A behavioural intervention to reduce excess weight gain	0-12 months		Body composition	September 2015

					during pregnancy through changing dietary intake, eating behaviour and PA			
Mottola et al. NCT02155751 NELIP trial	Canada	RCT	23	>34.9	Personalised dietary and PA program, the diet was similar to a diabetic meal plan and the PA included increased in walking	0-12 months	Infant growth	December 2017
Gallagher et al. NCT01616147 LIFT Trial*	USA	RCT	210	25-35	Counselling during pregnancy and group counselling after delivery regarding behaviour, nutrition, and PA change. Visits to counsellors occur twice monthly with additional weekly telephone and internet contacts.	0-12 months	Infant fat percentage at 14 and 52 weeks	December 2017 – data available (IJO, July 2019)
Atkinson et al. NCT01689961	Canada	RCT	350	< 40	The PA intervention was a custom-designed walking class of 30-60 min. 1x/week and a prescribed at-home walking program for 10,000 steps/day. The nutrition intervention was a high protein, low-fat dairy food plan designed to meet energy needs and with individualised counselling.	6 months	DXA	April 2019
Barakat et al. NCT02109588	Spain	RCT	1100	All	Supervised physical conditioning program of three 60-minute sessions per week during whole pregnancy.	0-24 months	BMI	April 2018
Renault et al. TOP Study NCT01345149	Denmark	RCT	425	>29.9	Mediterranean style diet consistent with national recommendations;	0-36 months	BMI	TBC

					increased PA measured by a pedometer.			
Bogaerts et al. Flanders	Belgium	RCT	205	>29.9	Dietary advice consistent with national guidelines	3 years	BMI	TBC
Dodd et al. LIMIT	Australia	RCT	2212	>24.9	Healthy eating in pregnancy, food substitutions, promote increased PA	3 years	BMI	TBC
Orth et al. NCT01841424 CO-OP trial	USA	RCT	100	>29.9	Dietary counselling. Maintain a food diary.	0-12 months	Weight	December 2019
Van Horn et al. NCT01631747 MOMFIT*	USA	RCT	281	25-35	Individual counselling sessions on diet and PA, daily tracking of diet and activity, and use of a pedometer.	0-12 months	Postnatal Weight development	July 2017
Koivusalo et al. NCT01698385 RADIEL	Finland	RCT	750	>29.9	Diet and exercise counselling, setting of specific goals, follow-up of achievements, laboratory tests and measurements.	0-10 years	Unknown	TBC
Thangaratinam et al. NCT02218931 ESTEEM	UK	RCT	3442	>29.9	The ESTEEM dietary pattern is similar to a Mediterranean diet associated with reduced risk of pre-eclampsia. The intervention will include structured meal plans and grocery lists, recipes for healthy diet and appropriate choices at restaurants.	Unknown	Unknown	April 2017
Vreugdenhil et al. NCT02703753 TOP-mums	Netherlands	RCT	112	>24.9	The intervention consists of a healthy diet, appropriate physical activity and, if applicable, smoking cessation, customised to the needs of the women.	0-12 months	Unknown	December 2020

Redman et al. NCT01610752 Expecting Success*	USA	RCT	54	>24.9	A 3-arm trial, participants are assigned to either SmartMoms, delivered in person at a SmartMoms-Clinic. Or through a smartphone app, Smartmoms-Phone. The intervention includes lessons, diet and behaviour change, delivered weekly through the 2nd trimester and semi-weekly throughout the 3rd trimester.	0-12 months	Postnatal weight development	TBC
Herring et al. NCT02229708	USA	RCT	262	25-45	An individual, technology-based behavioural intervention program which will include specific information about nutrition and PA, and strategies for helping them make changes to their diet, PA, and weight-related behaviours during.	0-12 months	Postnatal weight development	July 2019
Thomson et al. NCT01746394 Delta Healthy Sprouts	USA	RCT	82	All	Participants in the intervention arm will receive the enhanced diet and activity during pregnancy, infancy, and early childhood through a home visiting program.	0-12 months	BMI	May 2016
Wilcox et al. NCT02260518 HIPP	USA	RCT	400	25-45	The intervention will focus on women gaining the recommended amount of weight, increasing PA to 150 minutes per week, and meeting healthy eating guidelines.	12 months	Adiposity	October 2020

Phelan et al. NCT01545934 Healthy beginnings*	USA	RCT	350	>24.9	The intervention is a multicomponent program designed to prevent excessive GWG through modifications of diet, PA and behavioural strategies during pregnancy.	0-12 months	weight for age z scores	June 2021
Puder et al. NCT02890693 MySweetHeart	Switzerland	RCT	200	All	The intervention will consist of individual and group sessions with different members of the interdisciplinary team (dietician, physiotherapist, clinical psychologist or coach) During pregnancy and during the first year postpartum	0-12 months	Body composition	September 2020
Knowler et al. NCT01812694 LIFE-Moms Phoenix*	USA	RCT	1500	All	Individualised GWG goals, using both group and individual sessions, participants are encouraged to monitor dietary intake and increase daily PA.	0-12 months	Postnatal growth development	March 2017
Uauy et al. NCT01916603 CHiMINCs	Chile	Cluster-RCT	2400	All	Normative intervention on diet & PA & breastfeeding: diet and physical activity counselling-support and breastfeeding promotion till 12 months postpartum.	0-12 months	Postnatal growth development	March 2017

BMI, body mass index; DXA, dual-energy x-ray absorptiometry; GI, glycaemic index; GWG, gestational weight gain; PA, physical activity; SCSF, subscapular skinfold thickness; *The LIFE-Moms Research Group

Appendix 2: Electronic search criteria

MEDLINE and EMBASE

(1974-4th July 2017)

(P) Patient

#1 pregnancy/

#2 pregancy.mp.

#3 pregnan*.tw.

#4 gestation/

#5 maternal.mp.

#6 weight gain/

#7 exp body composition/

#8 exp body mass index/

#9 body size/

#10 exp animals/ not humans.sh.

(I) Intervention

#11 exp Diet/

#12 Randomi*ed controlled trial.pt

#13 Control* clinical trial.pt

#14 education/ or education.mp.

#15 counceling/ or counseling.mp.

#16 Energy Intake/ or dietary intake.mp.

#17 nutrition* advice/ or diet* advice.mp.

#18 low energy/ or low calorie.mp.

#19 glyc?emic index/ or glyc?emic load.mp.

#20 low carbohydrate.mp.

#21 low fat.mp.

#22 dietitian/ or dietician/ or nutritionist.mp.

#23 dietary assessment/ or dietary report.mp.

#24 diet* recall.mp.

#25 food frequency questionnaire.mp.

#26 food diary/ or food record/ or diet record.mp.

#27 health* eating.mp.

#28 Exp exercise/

#29 Physical therapy/ or physical activity.mp

(O) Outcomes

#30 Exp child/

#31 Exp infant/

#32 Child*/ or infan*.mp

#33 Follow?up.mp

#34 Body mass index/

#35 Obesity/ or exp pediatric obesity/

#36 Exp body weights and measures/

(C) Combination

#37 #1 OR #2 OR #3 OR #4 OR #5

#38 #6 OR #7 OR #8 OR #9

#39 #11 OR #12 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

#40 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

#41 #37 AND #38 AND #39 AND #40

#42 #41 NOT #10

#43 Limit #42 to yr=1990:current

Articles cited in MEDLINE: 2967

Articles cited in EMBASE: 218

Cochrane CENTRAL Register of Controlled Trials

#1 pregnan*

#2 gestation

#3 weight gain

#4 body mass index

#5 randomised controlled trial

#6 diet

#7 lifestyle

#8	physical activity
#9	intervention
#10	Infant
#11	child
#12	body composition
#13	animal not human
#14	#1 OR #2
#15	#3 OR #4
#16	#5 OR #6 OR #7 OR #8 OR #9
#17	#10 OR #11 OR #12
#18	#14 AND #15 AND #16 AND #17
#19	#18 NOT #13

Articles cited in Cochrane: 380

Appendix 3: NMR metabolic measures

Molecular class	Lipid, lipoprotein or metabolite name	Units*
Extremely large VLDL	Concentration of chylomicrons and extremely large VLDL particles	mol/l
	Total lipids in chylomicrons and extremely large VLDL	mmol/l
	Phospholipids in chylomicrons and extremely large VLDL	mmol/l
	Total cholesterol in chylomicrons and extremely large VLDL	mmol/l
	Free cholesterol in chylomicrons and extremely large VLDL	mmol/l
	Triglycerides in chylomicrons and extremely large VLDL	mmol/l
Very large VLDL	Concentration of very large VLDL particles	mol/l
	Total lipids in very large VLDL	mmol/l
	Phospholipids in very large VLDL	mmol/l
	Total cholesterol in very large VLDL	mmol/l
	Cholesterol esters in very large VLDL	mmol/l
	Free cholesterol in very large VLDL	mmol/l
	Triglycerides in very large VLDL	mmol/l
Large VLDL	Concentration of large VLDL particles	mol/l
	Total lipids in large VLDL	mmol/l
	Phospholipids in large VLDL	mmol/l
	Total cholesterol in large VLDL	mmol/l l
	Cholesterol esters in large VLDL	mmol/l
	Free cholesterol in large VLDL	mmol/l
	Triglycerides in large VLDL	mmol/l
Medium VLDL	Concentration of large VLDL particles	mol/l
	Total lipids in small VLDL	mmol/l
	Phospholipids in small VLDL	mmol/l
	Total cholesterol in small VLDL	mmol/l
	Cholesterol esters in small VLDL	mmol/l
	Free cholesterol in small VLDL	mmol/l
	Triglycerides in small VLDL	mmol/l
Small VLDL	Concentration of very small VLDL particles	mol/l
	Total lipids in very small VLDL	mmol/l
	Phospholipids in very small VLDL	mmol/l
	Total cholesterol in very small VLDL	mmol/l
	Cholesterol esters in very small VLDL	mmol/l
	Free cholesterol in very small VLDL	mmol/l
	Triglycerides in very small VLDL	mmol/l
IDl	Concentration of IDL particles	mol/l
	Total lipids in IDL	mmol/l
	Phospholipids in IDL	mmol/l
	Total cholesterol in IDL	mmol/l
	Cholesterol esters in IDL	mmol/l
	Free cholesterol in IDL	mmol/l
	Triglycerides in IDL	mmol/l
Large LDL	Concentration of large LDL particles	mol/l
	Total lipids in large LDL	mmol/l
	Phospholipids in large LDL	mmol/l
	Total cholesterol in large LDL	mmol/l
	Cholesterol esters in large LDL	mmol/l
	Free cholesterol in large LDL	mmol/l
	Triglycerides in large LDL	mmol/l

NMR metabolic profiles continued

Molecular class	Lipid, lipoprotein or metabolite name	Units*
Medium LDL	Concentration of medium LDL particles	mol/l
	Total lipids in medium LDL	mmol/l
	Phospholipids in medium LDL	mmol/l
	Total cholesterol in medium LDL	mmol/l
	Cholesterol esters in medium LDL	mmol/l
	Free cholesterol in medium LDL	mmol/l
	Triglycerides in medium LDL	mmol/l
Small LDL	Concentration of small LDL particles	mol/l
	Total lipids in small LDL	mmol/l
	Phospholipids in small LDL	mmol/l
	Total cholesterol in small LDL	mmol/l
	Cholesterol esters in small LDL	mmol/l
	Free cholesterol in small LDL	mmol/l
	Triglycerides in small LDL	mmol/l
Very large HDL	Concentration of very large HDL particles	mol/l
	Total lipids in very large HDL	mmol/l
	Phospholipids in very large HDL	mmol/l
	Total cholesterol in very large HDL	mmol/l
	Cholesterol esters in very large HDL	mmol/l
	Free cholesterol in very large HDL	mmol/l
	Triglycerides in very large HDL	mmol/l
Large HDL	Concentration of large HDL particles	mol/l
	Total lipids in large HDL	mmol/l
	Phospholipids in large HDL	mmol/l
	Total cholesterol in large HDL	mmol/l
	Cholesterol esters in large HDL	mmol/l
	Free cholesterol in large HDL	mmol/l
	Triglycerides in large HDL	mmol/l
Medium HDL	Concentration of medium HDL particles	mol/l
	Total lipids in medium HDL	mmol/l
	Phospholipids in medium HDL	mmol/l
	Total cholesterol in medium HDL	mmol/l
	Cholesterol esters in medium HDL	mmol/l
	Free cholesterol in medium HDL	mmol/l
	Triglycerides in medium HDL	mmol/l
Small HDL	Concentration of small HDL particles	mol/l
	Total lipids in small HDL	mmol/l
	Phospholipids in small HDL	mmol/l
	Total cholesterol in small HDL	mmol/l
	Cholesterol esters in small HDL	mmol/l
	Free cholesterol in small HDL	mmol/l
	Triglycerides in small HDL	mmol/l
Lipoprotein particle size	Mean diameter for VLDL particles	nm
	Mean diameter for LDL particles	nm
	Mean diameter for HDL particles	nm

NMR metabolic profiles continued

Molecular class	Lipid, lipoprotein or metabolite name	Units*
Cholesterol concentrations	Total cholesterol	mmol/l
	Total cholesterol in VLDL	mmol/l
	Remnant cholesterol (non-HDL and non-LDL cholesterol)	mmol/l
	Total cholesterol in LDL	mmol/l
	Total cholesterol in HDL	mmol/l
	Total cholesterol in HDL2	mmol/l
	Total cholesterol in HDL3	mmol/l
	Esterified cholesterol	mmol/l
	Free cholesterol	mmol/l
Glycerides and phospholipid concentrations (and one ratio)	Total triglycerides	mmol/l
	Triglycerides in VLDL	mmol/l
	Triglycerides in LDL	mmol/l
	Triglycerides in HDL	mmol/l
	Total phosphoglycerides	mmol/l
	Ratio of triglycerides to phosphoglycerides	
	Phosphatydilcholine and other cholines	mmol/l
	Sphingomyelins	mmol/l
	Total cholines	mmol/l
Apolipoprotein concentrations (and one ratio)	Apolipoprotein A-1	g/l
	Apolipoprotein B	g/l
	Ratio of apolipoprotein B to apolipoprotein A-1	
Fatty acid concentrations	Total fatty acids	mmol/l
	Estimated degree of saturation	
	22:6, docosahexaenoic acid	mmol/l
	18:2 linoleic acid	mmol/l
	Omega-3 fatty acids	mmol/l
	Omega-6 fatty acids	mmol/l
	Polyunsaturated fatty acids	mmol/l
	Monounsaturated fatty acids; 16:1, 18:1	mmol/l
	Saturated fatty acids	mmol/l
Fatty acid ratios	Ratio of 22:6, docosahexaenoic acid to total fatty acids	%
	Ratio of 18:2 linoleic acid to total fatty acids	%
	Ratio of omega-3 fatty acids to total fatty acids	%
	Ratio of omega-6 fatty acids to total fatty acids	%
	Ratio of polyunsaturated fatty acids to total fatty acids	%
	Ratio of monounsaturated fatty acids to total fatty acids	%
	Ratio of saturated fatty acids to total fatty acids	%
Glycolysis related metabolite	Glucose	mmol/l
	Lactate	mmol/l
	Pyruvate	mmol/l
	Citrate	mmol/l
	Glycerol	mmol/l

NMR metabolic profiles continued

Molecular class	Lipid, lipoprotein or metabolite name	Units*
Amino acid concentrations	Alanine	mmol/l
	Glutamine	mmol/l
	Glycine	mmol/l
	Histidine	mmol/l
branched	Isoleucine	mmol/l
branched	Leucine	mmol/l
branched	Valine	mmol/l
aromatic	Phenylalanine	mmol/l
aromatic	Tyrosine	mmol/l
Ketone body concentrations	Acetate	mmol/l
	Acetoacetate	mmol/l
	3-hydroxybutyrate	mmol/l
Fluid balance marker	Albumin	mmol/l
	Creatinine	mmol/l
Inflammation marker	Glycoprotein acetyls, mainly a1-acid glycoprotein	mmol/l

** These are the units used for each of the metabolic measures, unless we state that we are presenting results in standard deviation (SD) units. Where we present results that are the mean (in control participants) at 16-weeks these are the units. Where we present change in metabolic marker (between 16- to 36-weeks) or difference in change of metabolic markers the units are those listed in the table above per one week of gestational age. VLDL: very low-density lipoprotein; LDL: low density lipoprotein; IDL: intermediate density lipoprotein; HDL: high density lipoprotein*

References

Abbasi, A., Juszczyk, D., Jaarsveld, V., M, C.H., and Gulliford, M.C. (2017). Body Mass Index and Incident Type 1 and Type 2 Diabetes in Children and Young Adults: A Retrospective Cohort Study. J. Endocr. Soc. 1, 524–537.

Adamo, K.B., Ferraro, Z.M., and Brett, K.E. (2012). Can We Modify the Intrauterine Environment to Halt the Intergenerational Cycle of Obesity? Int. J. Environ. Res. Public. Health 9, 1263–1307.

Afshin, A., Forouzanfar, M.H., Reitsma, M.B., Sur, P., Estep, K., Lee, A., Marczak, L., Mokdad, A.H., Moradi-Lakeh, M., and Naghavi, M. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N. Engl. J. Med. 377, 13–27.

Aguilera, C.M., Olza, J., and Gil, Á. (2013). Genetic susceptibility to obesity and metabolic syndrome in childhood. Nutr. Hosp. 28, 44–55.

Ainsworth, B.E., Haskell, W.L., Whitt, M.C., Irwin, M.L., Swartz, A.M., Strath, S.J., O'Brien, W.L., Bassett, D.R., Schmitz, K.H., Emplaincourt, P.O., et al. (2000). Compendium of physical activities: an update of activity codes and MET intensities. Med. Sci. Sports Exerc. 32, S498-504.

Akoumianakis, I., and Antoniades, C. (2017). The interplay between adipose tissue and the cardiovascular system: is fat always bad? Cardiovasc. Res. 113, 999–1008.

Ambrosini, G.L. (2014). Childhood dietary patterns and later obesity: a review of the evidence. Proc. Nutr. Soc. 73, 137–146.

Antman, E.M., Lau, J., Kupelnick, B., Mosteller, F., and Chalmers, T.C. (1992). A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 268, 240–248.

Arenz, S., Rückerl, R., Koletzko, B., and von Kries, R. (2004). Breast-feeding and childhood obesity - a systematic review. Int. J. Obes. 28, 1247.

Ashcroft, J., Semmler, C., Carnell, S., van Jaarsveld, C.H.M., and Wardle, J. (2008). Continuity and stability of eating behaviour traits in children. Eur. J. Clin. Nutr. 62, 985–990.

Bain, E., Crane, M., Tieu, J., Han, S., Crowther, C.A., and Middleton, P. (2015). Diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Database Syst. Rev. 12.

Bandura, A. (2004). Health promotion by social cognitive means. Health Educ. Behav. Off. Publ. Soc. Public Health Educ. 31, 143–164.

Barker, D.J. (1995). Fetal origins of coronary heart disease. Br. Med. J. 311, 171.

Bellinger, L., Lilley, C., and Langley-Evans, S.C. (2004). Prenatal exposure to a maternal low-protein diet programmes a preference for high-fat foods in the young adult rat. Br. J. Nutr. 92, 513–520.

Beyerlein, A., and von Kries, R. (2011). Breastfeeding and body composition in children: will there ever be conclusive empirical evidence for a protective effect against overweight? Am. J. Clin. Nutr. 94, 1772S–1775S.

Beyerlein, A., Nehring, I., Rzehak, P., Heinrich, J., Müller, M.J., Plachta-Danielzik, S., Wabitsch, M., Weck, M., Brenner, H., Rothenbacher, D., et al. (2012). Gestational weight gain and body mass index in children: results from three german cohort studies. PloS One 7, e33205.

Bingham, S.A., Welch, A.A., McTaggart, A., Mulligan, A.A., Runswick, S.A., Luben, R., Oakes, S., Khaw, K.T., Wareham, N., and Day, N.E. (2001). Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. Public Health Nutr. 4, 847–858.

Birch, L., Savage, J.S., and Ventura, A. (2007). Influences on the Development of Children's Eating Behaviours: From Infancy to Adolescence. Can. J. Diet. Pract. Res. Publ. Dietit. Can. 68, s1–s56.

Bjerregaard, L.G., Jensen, B.W., Ängquist, L., Osler, M., Sørensen, T.I.A., and Baker, J.L. (2018). Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes. N. Engl. J. Med. 378, 1302–1312.

Blake-Lamb, T.L., Locks, L.M., Perkins, M.E., Woo Baidal, J.A., Cheng, E.R., and Taveras, E.M. (2016). Interventions for childhood obesity in the first 1,000 days a systematic review. Am. J. Prev. Med. 50, 780–789.

Blauw, L.L., Noordam, R., Trompet, S., Berbée, J.F.P., Rosendaal, F.R., Heemst, D. van, Dijk, K.W. van, Mook-Kanamori, D.O., Mutsert, R. de, and Rensen, P.C.N. (2017). Genetic variation in the obesity gene FTO is not associated with decreased fat oxidation: the NEO study. Int. J. Obes. 41, 1594–1600.

Blüher, M. (2019). Obesity: global epidemiology and pathogenesis. Nat. Rev. Endocrinol. 15, 288–298.

Bogaerts, A.F., Devlieger, R., Nuyts, E., Witters, I., Gyselaers, W., and Van den Bergh, B.R. (2013). Effects of lifestyle intervention in obese pregnant women on gestational weight gain and mental health: a randomized controlled trial. Int. J. Obes. 37, 814–821.

Boswell, N., Byrne, R., and Davies, P.S.W. (2018). Eating behavior traits associated with demographic variables and implications for obesity outcomes in early childhood. Appetite 120, 482–490.

Boswell, N., Byrne, R., and Davies, P.S.W. (2019). Family food environment factors associated with obesity outcomes in early childhood. BMC Obes. 6, 17.

Breij, L.M., Mulder, M.T., van Vark-van der Zee, L.C., and Hokken-Koelega, A.C.S. (2017). Appetite-regulating hormones in early life and relationships with type of feeding and body composition in healthy term infants. Eur. J. Nutr. 56, 1725–1732.

Briley, A.L., Barr, S., Badger, S., Bell, R., Croker, H., Godfrey, K.M., Holmes, B., Kinnunen, T.I., Nelson, S.M., Oteng-Ntim, E., et al. (2014). A complex intervention to improve pregnancy

outcome in obese women; the UPBEAT randomised controlled trial. BMC Pregnancy Childbirth 14, 74.

Britton, K.A., Massaro, J.M., Murabito, J.M., Kreger, B.E., Hoffmann, U., and Fox, C.S. (2013). Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J. Am. Coll. Cardiol. 62, 921–925.

Butland, B., Jebb, S., Kopelman, P., McPherson, K., Thomas, S., Mardell, J., and Parry, V. (2007). Tackling obesities: future choices-project report (Department of Innovation, Universities and Skills London).

Cancer Research UK (2019). We Need Change.

Carnell, S., and Wardle, J. (2007). Measuring behavioural susceptibility to obesity: validation of the child eating behaviour questionnaire. Appetite 48, 104–113.

Castillo, H., Santos, I.S., and Matijasevich, A. (2015). Relationship between maternal pre-pregnancy body mass index, gestational weight gain and childhood fatness at 6–7 years by air displacement plethysmography. Matern. Child. Nutr. 11, 606–617.

Catalano, P.M., and Shankar, K. (2017). Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. Br. Med. J. 356, j1.

Catalano, P.M., Roman-Drago, N.M., Amini, S.B., and Sims, E.A. (1998). Longitudinal changes in body composition and energy balance in lean women with normal and abnormal glucose tolerance during pregnancy. Am. J. Obstet. Gynecol. 179, 156–165.

Catalano, P.M., Farrell, K., Thomas, A., Huston-Presley, L., Mencin, P., de Mouzon, S.H., and Amini, S.B. (2009). Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr 90, 1303–1313.

Choquet, H., and Meyre, D. (2011). Genetics of Obesity: What have we Learned? Curr. Genomics 12, 169–179.

Cnattingius, S., Villamor, E., Lagerros, Y.T., Wikström, A.-K., and Granath, F. (2012). High birth weight and obesity—a vicious circle across generations. Int. J. Obes. 36, 1320–1324.

Coelho, M., Oliveira, T., and Fernandes, R. (2013). Biochemistry of adipose tissue: an endocrine organ. Arch. Med. Sci. 9, 191–200.

Cole, T. (2004). Children grow and horses race: is the adiposity rebound a critical period for later obesity? BMC Pediatr. 4, 6.

Cole, T.J., and Lobstein, T. (2012). Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr. Obes. 7, 284–294.

Cooke, L., Wardle, J., and Gibson, E.. (2003). Relationship between parental report of food neophobia and everyday food consumption in 2–6-year-old children. Appetite 41, 205–206.

Cordova, A., Villa, G., Sureda, A., Rodriguez-Marroyo, J.A., and Sánchez-Collado, M.P. (2012). Physical Activity and Cardiovascular Risk Factors in Spanish Children Aged 11-13 Years. Rev. Esp. Cardiol. 65, 620–626.

Costello, A.B., and Osborne, J.W. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Pract. Assess. Res. Eval. 10, 173–178.

Cox, J.L., Holden, J.M., and Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry J. Ment. Sci. 150, 782–786.

Cunningham, S.A., Kramer, M.R., and Narayan, K.M.V. (2014). Incidence of childhood obesity in the United States. N. Engl. J. Med. 370, 403–411.

Dabelea, D., and Crume, T. (2011). Maternal environment and the transgenerational cycle of obesity and diabetes. Diabetes 60, 1849–1855.

Dalrymple, K.V., Flynn, A.C., Relph, S.A., O'Keeffe, M., and Poston, L. (2018a). Lifestyle Interventions in Overweight and Obese Pregnant or Postpartum Women for Postpartum Weight Management: A Systematic Review of the Literature. Nutrients 10, 1704.

Dalrymple, K.V., Martyni-Orenowicz, J., Flynn, A.C., Poston, L., and O'Keeffe, M. (2018b). Can antenatal diet and lifestyle interventions influence childhood obesity? A systematic review. Matern Child Nutr 14, e12628.

Dalrymple, K.V., Thompson, J.M.D., Begum, S., Godfrey, K.M., Poston, L., Seed, P.T., McCowan, L.M.E., Wall, C., Shelling, A., North, R., et al. (2019a). Relationships of maternal body mass index and plasma biomarkers with childhood body mass index and adiposity at 6 years: The Children of SCOPE study. Pediatr. Obes. e12537.

Dalrymple, K.V., Flynn, A.C., Seed, P.T., Briley, A.L., O'Keeffe, M., Godfrey, K.M., and Poston, L. (2019b). Associations between dietary patterns, eating behaviours, and body composition and adiposity in 3-year-old children of mothers with obesity. Pediatr. Obes. e12608.

Dalton, M., Cameron, A.J., Zimmet, P.Z., Shaw, J.E., Jolley, D., Dunstan, D.W., Welborn, T.A., and AusDiab Steering Committee (2003). Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J. Intern. Med. 254, 555–563.

Dangardt, F., Charakida, M., Georgiopoulos, G., Chiesa, S.T., Rapala, A., Wade, K.H., Hughes, A.D., Timpson, N.J., Pateras, K., Finer, N., et al. (2019). Association between fat mass through adolescence and arterial stiffness: a population-based study from The Avon Longitudinal Study of Parents and Children. Lancet Child Adolesc. Health 3, 474–481.

Davey Smith, G., Steer, C., Leary, S., and Ness, A. (2007). Is there an intrauterine influence on obesity? Evidence from parent child associations in the Avon Longitudinal Study of Parents and Children (ALSPAC). Arch Child 92, 876–880.

De Cosmi, V., Scaglioni, S., and Agostoni, C. (2017). Early Taste Experiences and Later Food Choices. Nutrients 9, 107.

Di Cesare, M., Sorić, M., Bovet, P., Miranda, J.J., Bhutta, Z., Stevens, G.A., Laxmaiah, A., Kengne, A.-P., and Bentham, J. (2019). The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC Med. 17, 212.

Di Genova, L., Penta, L., Biscarini, A., Di Cara, G., and Esposito, S. (2018). Children with Obesity and Asthma: Which Are the Best Options for Their Management? Nutrients 10.

Dietz, W.H. (2017). Time to Adopt New Measures of Severe Obesity in Children and Adolescents. Pediatrics 140, e20172148.

Dodd, J.M., Grivell, R.M., Crowther, C.A., and Robinson, J.S. (2010). Antenatal interventions for overweight or obese pregnant women: a systematic review of randomised trials. BJOG Int. J. Obstet. Gynaecol. 117, 1316–1326.

Dodd, J.M., Grivell, R.M., Louise, J., Deussen, A.R., Giles, L., Mol, B.W., Vinter, C., Tanvig, M., Jensen, D.M., and Bogaerts, A. (2017). The effects of dietary and lifestyle interventions among pregnant women who are overweight or obese on longer-term maternal and early childhood outcomes: protocol for an individual participant data (IPD) meta-analysis. Syst. Rev. 6, 51.

Donin, A.S., Nightingale, C.M., Owen, C.G., Rudnicka, A.R., McNamara, M.C., Prynne, C.J., Stephen, A.M., Cook, D.G., and Whincup, P.H. (2010). Ethnic differences in blood lipids and dietary intake between UK children of black African, black Caribbean, South Asian, and white European origin: the Child Heart and Health Study in England (CHASE). Am. J. Clin. Nutr. 92, 776–783.

Drake, A.J., and Reynolds, R.M. (2010). Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction 140, 387–398.

Druet, C., and Ong, K.K. (2008). Early childhood predictors of adult body composition. Best Pract. Res. Clin. Endocrinol. Metab. 22, 489–502.

Ebbeling, C.B., Pawlak, D.B., and Ludwig, D.S. (2002). Childhood obesity: public-health crisis, common sense cure. The Lancet 360, 473–482.

Eisenmann, J.C., Heelan, K.A., and Welk, G.J. (2004). Assessing body composition among 3- to 8-year-old children: Anthropometry, BIA, and DXA. Obes. Res. 12, 1633–1640.

Ekelund, U., Sepp, H., Brage, S., Becker, W., Jakes, R., Hennings, M., and Wareham, N.J. (2006). Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. Public Health Nutr. 9, 258–265.

Eloranta, A.-M., Lindi, V., Schwab, U., Tompuri, T., Kiiskinen, S., Lakka, H.-M., Laitinen, T., and Lakka, T.A. (2012). Dietary factors associated with overweight and body adiposity in Finnish children aged 6-8 years: the PANIC Study. Int. J. Obes. 2005 36, 950–955.

El-Sayed, A.M., Scarborough, P., and Galea, S. (2011). Ethnic inequalities in obesity among children and adults in the UK: a systematic review of the literature. Obes. Rev. Off. J. Int. Assoc. Study Obes. 12, e516-534.

Emmett, P.M., Hays, N.P., and Taylor, C.M. (2018). Antecedents of picky eating behaviour in young children. Appetite 130, 163–173.

Eriksson, J.G., Sandboge, S., Salonen, M.K., Kajantie, E., and Osmond, C. (2014). Long-term consequences of maternal overweight in pregnancy on offspring later health: Findings from the Helsinki Birth Cohort Study. Ann. Med. 46, 434–438.

Ernst, G. (2017). Heart-Rate Variability—More than Heart Beats? Front. Public Health 5, 240.
Ester, W.A., Jansen, P.W., Hoek, H.W., Verhulst, F.C., Jaddoe, V.W., Marques, A.H., Tiemeier, H., Susser, E.S., and Roza, S.J. (2019). Fetal size and eating behaviour in childhood: a prospective cohort study. Int. J. Epidemiol. 48, 124–133.

Fall, C.H. (2013). Fetal malnutrition and long-term outcomes. Nestle Nutr. Inst. Workshop Ser. 74, 11–25.

Fehlert, E., Willmann, K., Fritsche, L., Linder, K., Mat-Husin, H., Schleger, F., Weiss, M., Kiefer-Schmidt, I., Brucker, S., Häring, H.-U., et al. (2017). Gestational diabetes alters the fetal heart

rate variability during an oral glucose tolerance test: a fetal magnetocardiography study. BJOG Int. J. Obstet. Gynaecol. 124, 1891–1898.

Fernández-Alvira, J.M., Bammann, K., Eiben, G., Hebestreit, A., Kourides, Y.A., Kovacs, E., Michels, N., Pala, V., Reisch, L., Russo, P., et al. (2017). Prospective associations between dietary patterns and body composition changes in European children: the IDEFICS study. Public Health Nutr. 20, 3257–3265.

Ferranti, S. de, and Mozaffarian, D. (2008). The Perfect Storm: Obesity, Adipocyte Dysfunction, and Metabolic Consequences. Clin. Chem. 54, 945–955.

Fewtrell, M.S., Kennedy, K., Singhal, A., Martin, R.M., Ness, A., Hadders-Algra, M., Koletzko, B., and Lucas, A. (2008). How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch. Dis. Child. 93, 458–461.

Finer, L.B., and Zolna, M.R. (2011). Unintended pregnancy in the United States: incidence and disparities, 2006. Contraception 84, 478–485.

Fisk, C.M., Crozier, S.R., Inskip, H.M., Godfrey, K.M., Cooper, C., Robinson, S.M., and Southampton Women's Survey Study Group (2011). Influences on the quality of young children's diets: the importance of maternal food choices. Br. J. Nutr. 105, 287–296.

Fitzpatrick, E., and Dhawan, A. (2019). Childhood and Adolescent Nonalcoholic Fatty Liver Disease: Is It Different from Adults? J. Clin. Exp. Hepatol. 9, 716–722.

Flegal, K., and Cole, T. (2013). Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. Natl. Health Stat. Rep. 63, 1–3.

Fleten, C., Nystad, W., Stigum, H., Skjaerven, R., Lawlor, D.A., Davey Smith, G., and Naess, O. (2012). Parent-offspring body mass index associations in the Norwegian Mother and Child Cohort Study: a family-based approach to studying the role of the intrauterine environment in childhood adiposity. Am. J. Epidemiol. 176, 83–92.

Flynn, A.C., Dalrymple, K., Barr, S., Poston, L., Goff, L.M., Rogozińska, E., van Poppel, M.N., Rayanagoudar, G., Yeo, S., and Carballo, R.B. (2016a). Dietary interventions in overweight and obese pregnant women: a systematic review of the content, delivery, and outcomes of randomized controlled trials. Nutr. Rev. 74, 312–328.

Flynn, A.C., Seed, P.T., Patel, N., Barr, S., Bell, R., Briley, A.L., Godfrey, K.M., Nelson, S.M., Oteng-Ntim, E., Robinson, S.M., et al. (2016b). Dietary patterns in obese pregnant women; influence of a behavioral intervention of diet and physical activity in the UPBEAT randomized controlled trial. Int. J. Behav. Nutr. Phys. Act. 13, 124.

Flynn, A.C., Thompson, J.M.D., Dalrymple, K.V., Wall, C., Begum, S., Pallippadan Johny, J., Cutfield, W.S., North, R., McCowan, L.M.E., Godfrey, K.M., et al. (2020). Childhood dietary patterns and body composition at age 6 years: the Children of SCOPE study. Br. J. Nutr. 1–21.

Flynn, J.T., Kaelber, D.C., Baker-Smith, C.M., Blowey, D., Carroll, A.E., Daniels, S.R., Ferranti, S.D. de, Dionne, J.M., Falkner, B., Flinn, S.K., et al. (2017). Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 140, e20171904.

Fogel, A., Goh, A.T., Fries, L.R., Sadananthan, S.A., Velan, S.S., Michael, N., Tint, M.T., Fortier, M.V., Chan, M.J., Toh, J.Y., et al. (2017). Faster eating rates are associated with higher energy intakes during an Ad libitum meal, higher BMI and greater adiposity among 4.5 year old children – Results from the GUSTO cohort. Br. J. Nutr. 117, 1042–1051.

Fogel, A., McCrickerd, K., Aris, I.M., Goh, A.T., Chong, Y.-S., Tan, K.H., Yap, F., Shek, L.P., Meaney, M.J., Broekman, B.F.P., et al. (2020). Eating behaviors moderate the associations between risk factors in the first 1000 days and adiposity outcomes at 6 years of age. Am. J. Clin. Nutr. 111, 997–1006.

Franco, J.G., Fernandes, T.P., Rocha, C.P.D., Calviño, C., Pazos-Moura, C.C., Lisboa, P.C., Moura, E.G., and Trevenzoli, I.H. (2012). Maternal high-fat diet induces obesity and adrenal and thyroid dysfunction in male rat offspring at weaning. J. Physiol. 5503–5518.

Frayling, T.M., Timpson, N.J., Weedon, M.N., Zeggini, E., Freathy, R.M., Lindgren, C.M., Perry, J.R.B., Elliott, K.S., Lango, H., Rayner, N.W., et al. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316, 889–894.

Freedman, D.S., Butte, N.F., Taveras, E.M., Lundeen, E.A., Blanck, H.M., Goodman, A.B., and Ogden, C.L. (2017). BMI z-scores are a poor indicator of adiposity among 2- to 19-year-olds with very high BMIs, NHANES 1999-2000 to 2013-14. Obes. Silver Spring Md 25, 739–746.

Gaillard, R. (2015). Maternal obesity during pregnancy and cardiovascular development and disease in the offspring. Eur. J. Epidemiol. 30, 1141–1152.

Gaillard, R., Durmuş, B., Hofman, A., Mackenbach, J.P., Steegers, E.A., and Jaddoe, V.W. (2013). Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. Obesity 21, 1046–1055.

Gaillard, R., Steegers, E.A., Duijts, L., Felix, J.F., Hofman, A., Franco, O.H., and Jaddoe, V.W. (2014). Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. Hypertension 63, 683–691.

Gaillard, R., Steegers, E.A., Franco, O.H., Hofman, A., and Jaddoe, V.W. (2015). Maternal weight gain in different periods of pregnancy and childhood cardio-metabolic outcomes. The Generation R Study. Int. J. Obes. 39, 677–685.

Gaillard, R., Welten, M., Oddy, W.H., Beilin, L.J., Mori, T.A., Jaddoe, V.W.V., and Huang, R.-C. (2016a). Associations of maternal prepregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. BJOG Int. J. Obstet. Gynaecol. 207–216.

Gaillard, R., Santos, S., Duijts, L., and Felix, J.F. (2016b). Childhood Health Consequences of Maternal Obesity during Pregnancy: A Narrative Review. Ann. Nutr. Metab. 69, 171–180.

García, A.P., Palou, M., Priego, T., Sánchez, J., Palou, A., and Picó, C. (2010). Moderate caloric restriction during gestation results in lower arcuate nucleus NPY- and αMSH-neurons and

impairs hypothalamic response to fed/fasting conditions in weaned rats. Diabetes Obes. Metab. 12, 403–413.

Garcia-Vargas, L., Addison, S.S., Nistala, R., Kurukulasuriya, D., and Sowers, J.R. (2012). Gestational Diabetes and the Offspring: Implications in the Development of the Cardiorenal Metabolic Syndrome in Offspring. Cardiorenal Med. 2, 134–142.

Gardner, B., Wardle, J., Poston, L., and Croker, H. (2011). Changing diet and physical activity to reduce gestational weight gain: a meta-analysis. Obes. Rev. 12.

Gartstein, M.A., and Rothbart, M.K. (2003). Studying infant temperament via the Revised Infant Behavior Questionnaire. Infant Behav. Dev. 26, 64–86.

GBD Obesity Collaborators (2017). Health effects of overweight and obesity in 195 countries over 25 years. N. Engl. J. Med. 377, 13–27.

Geserick, M., Vogel, M., Gausche, R., Lipek, T., Spielau, U., Keller, E., Pfäffle, R., Kiess, W., and Körner, A. (2018). Acceleration of BMI in Early Childhood and Risk of Sustained Obesity. N. Engl. J. Med. 379, 1303–1312.

Gillman, M.W. (2012). Gestational weight gain: now and the future. Circulation 125, 1339–1340.

Gillman, M.W., and Poston, L. (2012). Maternal Obesity (Cambridge: Cambridge University Press).

Gillman, M.W., Rifas-Shiman, S.L., Kleinman, K., Oken, E., Rich-Edwards, J.W., and Taveras, E.M. (2008). Developmental Origins of Childhood Overweight: Potential Public Health Impact. Obesity 16, 1651–1656.

Gluckman, P.D., Hanson, M.A., Spencer, H.G., and Bateson, P. (2005). Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. Proc. R. Soc. B Biol. Sci. 272, 671–677.

Godfrey, K.M., Gluckman, P.D., and Hanson, M.A. (2010). Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol. Metab. 21, 199–205.

Godfrey, K.M., Costello, P.M., and Lillycrop, K.A. (2016). Development, Epigenetics and Metabolic Programming. Nestle Nutr. Inst. Workshop Ser. 85, 71–80.

Godfrey, K.M., Reynolds, R.M., Prescott, S.L., Nyirenda, M., Jaddoe, V.W., Eriksson, J.G., and Broekman, B.F. (2017). Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol 5, 53–64.

Goltz, F.R., Thackray, A.E., Varela-Mato, V., King, J.A., Dorling, J.L., Dowejko, M., Mastana, S., Thompson, J., Atkinson, G., and Stensel, D.J. (2019). Exploration of associations between the FTO rs9939609 genotype, fasting and postprandial appetite-related hormones and perceived appetite in healthy men and women. Appetite 142, 104368.

Goodman, R., Meltzer, H., and Bailey, V. (1998). The Strengths and Difficulties Questionnaire: a pilot study on the validity of the self-report version. Eur. Child Adolesc. Psychiatry 7, 125–130.

Gormally, J., Black, S., Daston, S., and Rardin, D. (1982). The assessment of binge eating severity among obese persons. Addict. Behav. 7, 47–55.

Graham, J.W., and Donaldson, S.I. (1993). Evaluating interventions with differential attrition: The importance of nonresponse mechanisms and use of follow-up data. J. Appl. Psychol. 78, 119–128.

Guh, D.P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C.L., and Anis, A.H. (2009). The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health 9, 88.

Han, J.C., Lawlor, D.A., and Kimm, S.Y. (2010). Childhood obesity. The Lancet 375, 1737–1748.

Hankinson, A.L., Daviglus, M.L., Bouchard, C., Carnethon, M., Lewis, C.E., Schreiner, P.J., Liu, K., and Sidney, S. (2010). Maintaining a high physical activity level over 20 years and weight gain. JAMA 304, 2603–2610.

Hao, G., Wang, X., Treiber, F.A., Harshfield, G., Kapuku, G., and Su, S. (2018). Body mass index trajectories in childhood is predictive of cardiovascular risk: results from the 23-year longitudinal Georgia Stress and Heart study. Int. J. Obes. 42, 923–925.

Harder, T., Bergmann, R., Kallischnigg, G., and Plagemann, A. (2005). Duration of breastfeeding and risk of overweight: a meta-analysis. Am. J. Epidemiol. 162, 397–403.

Hawkins, S.S., Baum, C.F., Rifas-Shiman, S.L., Oken, E., and Taveras, E.M. (2019). Examining Associations between Perinatal and Postnatal Risk Factors for Childhood Obesity Using Sibling Comparisons. Child. Obes. 15, 254–261.

Helmo, F.R., and Moed, A.M. (2007). Angiogenic and antiangiogenic factors in preeclampsia. Matern Child Health J 11, 199–206.

Heslehurst, N., Rankin, J., Wilkinson, J.R., and Summerbell, C.D. (2010). A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int. J. Obes. 2005 34, 420–428.

Heslehurst, N., Vieira, R., Akhter, Z., Bailey, H., Slack, E., Ngongalah, L., Pemu, A., and Rankin, J. (2019). The association between maternal body mass index and child obesity: A systematic review and meta-analysis. PLOS Med. 16, e1002817.

Hidaka, B.H., Kerling, E.H., Thodosoff, J.M., Sullivan, D.K., Colombo, J., and Carlson, S.E. (2016). Dietary patterns of early childhood and maternal socioeconomic status in a unique prospective sample from a randomized controlled trial of Prenatal DHA Supplementation. BMC Pediatr. 16, 191.

Higgins, J., and Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.

Hill, J.O., Wyatt, H.R., and Peters, J.C. (2012). Energy Balance and Obesity. Circulation 126, 126–132.

Hinkle, S.N., Sharma, A.J., Swan, D.W., Schieve, L.A., Ramakrishnan, U., and Stein, A.D. (2012). Excess gestational weight gain is associated with child adiposity among mothers with normal and overweight prepregnancy weight status. J. Nutr. 142, 1851–1858.

Hoffman, D.J., Reynolds, R.M., and Hardy, D.B. (2017). Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr. Rev. 75, 951–970.

Horan, M.K., McGowan, C.A., Gibney, E.R., Byrne, J., Donnelly, J.M., and McAuliffe, F.M. (2016). Maternal Nutrition and Glycaemic Index during Pregnancy Impacts on Offspring Adiposity at 6 Months of Age--Analysis from the ROLO Randomised Controlled Trial. Nutrients 8, 04.

Hörnell, A., Lagström, H., Lande, B., and Thorsdottir, I. (2013). Protein intake from 0 to 18 years of age and its relation to health: a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nutr. Res. 57.

Howell, K.R., and Powell, T.L. (2017). Effects of maternal obesity on placental function and fetal development. Reprod. Camb. Engl. 153, R97–R108.

Hruby, A., and Hu, F.B. (2015). The Epidemiology of Obesity: A Big Picture. Pharm. Econ. 33, 673–689.

Hruby, A., Manson, J.E., Qi, L., Malik, V.S., Rimm, E.B., Sun, Q., Willett, W.C., and Hu, F.B. (2016). Determinants and Consequences of Obesity. Am. J. Public Health 106, 1656–1662.

Hu, F.B. (2002). Dietary pattern analysis: a new direction in nutritional epidemiology. Curr. Opin. Lipidol. 13, 3–9.

Huang, T., and Hu, F.B. (2015). Gene-environment interactions and obesity: recent developments and future directions. BMC Med. Genomics 8, S2.

Huang, J.S., Lee, T.A., and Lu, M.C. (2007). Prenatal Programming of Childhood Overweight and Obesity. Matern. Child Health J. 11, 461–473.

Husin, H.M., Schleger, F., Bauer, I., Fehlert, E., Kiefer-Schmidt, I., Weiss, M., Kagan, K.O., Brucker, S., Pauluschke-Fröhlich, J., Eswaran, H., et al. (2020). Maternal Weight, Weight Gain, and Metabolism are Associated with Changes in Fetal Heart Rate and Variability. Obesity 28, 114–121.

Institute of Medicine (2009). The National Academies Collection: Reports funded by National Institutes of Health. In Weight Gain During Pregnancy: Reexamining the Guidelines, K.M. Rasmussen, and A.L. Yaktine, eds. (Washington (DC)).

i-WIP Collaborative Group (2017). i-WIP Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. BMJ 358, j3119.

van Jaarsveld, C.H., and Gulliford, M.C. (2015). Childhood Obesity Trends from Primary Care Electronic Health Records in England between 1994 and 2013. Arch. Dis. Child. 100, 214–219.
van Jaarsveld, C.H., Boniface, D., Llewellyn, C.H., and Wardle, J. (2014). Appetite and growth: a longitudinal sibling analysis. JAMA Pediatr. 168, 345–350.

Jansen, A., Theunissen, N., Slechten, K., Nederkoorn, C., Boon, B., Mulkens, S., and Roefs, A. (2003). Overweight children overeat after exposure to food cues. Eat. Behav. 4, 197–209.

Jarman, M., Fisk, C., Ntani, G., Crozier, S., Godfrey, K., Inskip, H., Cooper, C., and Robinson, S. (2014). Assessing diets of 3 year old children: evaluation of a food frequency questionnaire. Public Health Nutr. 17, 1069–1077.

Jensen, S.M., Mølgaard, C., Ejlerskov, K.T., Christensen, L.B., Michaelsen, K.F., and Briend, A. (2015). Validity of anthropometric measurements to assess body composition, including muscle mass, in 3-year-old children from the SKOT cohort. Matern. Child. Nutr. 11, 398–408.

Jharap, V.V., Santos, S., Steegers, E.A.P., Jaddoe, V.W.V., and Gaillard, R. (2017). Associations of maternal obesity and excessive weight gain during pregnancy with subcutaneous fat mass in infancy. Early Hum Dev 108, 23–28.

Johnson, L., van Jaarsveld, C.H.M., Llewellyn, C.H., Cole, T.J., and Wardle, J. (2014). Associations between infant feeding and the size, tempo and velocity of infant weight gain: SITAR analysis of the Gemini twin birth cohort. Int. J. Obes. 2005 38, 980–987.

Karachaliou, M., Georgiou, V., Roumeliotaki, T., Chalkiadaki, G., Daraki, V., Koinaki, S., Dermitzaki, E., Sarri, K., Vassilaki, M., and Kogevinas, M. (2015). Association of trimester-specific gestational weight gain with fetal growth, offspring obesity, and cardiometabolic traits in early childhood. Am. J. Obstet. Gynecol. 212, 502. e1-502. e14.

Keller, K.L., Kling, S.M.R., Fuchs, B., Pearce, A.L., Reigh, N.A., Masterson, T., and Hickok, K. (2019). A Biopsychosocial Model of Sex Differences in Children's Eating Behaviors. Nutrients 11.

Kepper, M., Tseng, T.-S., Volaufova, J., Scribner, R., Nuss, H., and Sothern, M. (2016). Pre-school obesity is inversely associated with vegetable intake, grocery stores and outdoor play. Pediatr. Obes. 11, e6–e8.

Kinnunen, T., Pasanen, M., Aittasalo, M., Fogelholm, M., Hilakivi-Clarke, L., Weiderpass, E., and Luoto, R. (2007). Preventing excessive weight gain during pregnancy–a controlled trial in primary health care. Eur. J. Clin. Nutr. 61, 884–891.

Kirk, S.L., Samuelsson, A.-M., Argenton, M., Dhonye, H., Kalamatianos, T., Poston, L., Taylor, P.D., and Coen, C.W. (2009). Maternal obesity induced by diet in rats permanently influences central processes regulating food intake in offspring. PloS One 4, e5870.

Koletzko, B., von Kries, R., Monasterolo, R.C., Subías, J.E., Scaglioni, S., Giovannini, M., Beyer, J., Demmelmair, H., Anton, B., and Gruszfeld, D. (2009a). Can infant feeding choices modulate later obesity risk? Am. J. Clin. Nutr. 89, 1502S–1508S.

Koletzko, B., von Kries, R., Closa, R., Escribano, J., Scaglioni, S., Giovannini, M., Beyer, J., Demmelmair, H., Gruszfeld, D., Dobrzanska, A., et al. (2009b). Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. Am. J. Clin. Nutr. 89, 1836–1845.

Koletzko, B., Brands, B., Poston, L., Godfrey, K., and Demmelmair, H. (2012). Early nutrition programming of long-term health. Proc. Nutr. Soc. 71, 371–378.

Kolu, P., Raitanen, J., Puhkala, J., Tuominen, P., Husu, P., and Luoto, R. (2016). Effectiveness and cost-effectiveness of a cluster-randomized prenatal lifestyle counseling trial: A seven-year follow-up. PLoS ONE 11 (12).

Kramer, M.S., Chalmers, B., Hodnett, E.D., Sevkovskaya, Z., Dzikovich, I., Shapiro, S., Collet, J.P., Vanilovich, I., Mezen, I., Ducruet, T., et al. (2001). Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA 285, 413–420.

Kristiansen, A.L., Bjelland, M., Brantsæter, A.L., Haugen, M., Meltzer, H.M., Nystad, W., and Andersen, L.F. (2015). Tracking of body size from birth to 7 years of age and factors associated with maintenance of a high body size from birth to 7 years of age – the Norwegian Mother and Child Cohort study (MoBa). Public Health Nutr. 18, 1746–1755.

Kumar, S., and Kelly, A.S. (2017). Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin. Proc. 92, 251–265.

Kuntz, B., and Lampert, T. (2010). Socioeconomic Factors and Obesity. Dtsch. Ärztebl. Int. 107, 517–522.

Lafraire, J., Rioux, C., Giboreau, A., and Picard, D. (2016). Food rejections in children: Cognitive and social/environmental factors involved in food neophobia and picky/fussy eating behavior. Appetite 96, 347–357.

Laitinen, J., Jääskeläinen, A., Hartikainen, A., Sovio, U., Vääräsmäki, M., Pouta, A., Kaakinen, M., and Järvelin, M. (2012). Maternal weight gain during the first half of pregnancy and

offspring obesity at 16 years: a prospective cohort study. BJOG Int. J. Obstet. Gynaecol. 119, 716–723.

Lamerz, A., Kuepper-Nybelen, J., Wehle, C., Bruning, N., Trost-Brinkhues, G., Brenner, H., Hebebrand, J., and Herpertz-Dahlmann, B. (2005). Social class, parental education, and obesity prevalence in a study of six-year-old children in Germany. Int. J. Obes. 2005 29, 373–380.

Langley-Evans, S.C. (2004). Fetal Nutrition and Adult Disease: Programming of Chronic Disease Through Fetal Exposure to Undernutrition (CABI).

Langley-Evans, S.C., Bellinger, L., and McMullen, S. (2005). Animal models of programming: early life influences on appetite and feeding behaviour. Matern. Child. Nutr. 1, 142–148.

de Lauzon, B., Romon, M., Deschamps, V., Lafay, L., Borys, J.-M., Karlsson, J., Ducimetière, P., Charles, M.A., and Fleurbaix Laventie Ville Sante Study Group (2004). The Three-Factor Eating Questionnaire-R18 is able to distinguish among different eating patterns in a general population. J. Nutr. 134, 2372–2380.

Lawlor, D.A., Smith, G.D., O'Callaghan, M., Alati, R., Mamun, A.A., Williams, G.M., and Najman, J.M. (2007). Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. Am J Epidemiol 165, 418–424.

Lawlor, D.A., Fraser, A., Lindsay, R.S., Ness, A., Dabelea, D., Catalano, P., Davey Smith, G., Sattar, N., and Nelson, S.M. (2010). Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia 53, 89–97.

Lawlor, D.A., Lichtenstein, P., Fraser, A., and Långström, N. (2011). Does maternal weight gain in pregnancy have long-term effects on offspring adiposity? A sibling study in a prospective cohort of 146,894 men from 136,050 families. Am. J. Clin. Nutr. 94, 142–148.

Lawlor, D.A., Relton, C., Sattar, N., and Nelson, S.M. (2012). Maternal adiposity—a determinant of perinatal and offspring outcomes? Nat. Rev. Endocrinol. 8, 679–688.

Leddy, M.A., Power, M.L., and Schulkin, J. (2008). The Impact of Maternal Obesity on Maternal and Fetal Health. Rev. Obstet. Gynecol. 1, 170–178.

Lee, K.W., Ching, S.M., Ramachandran, V., Yee, A., Hoo, F.K., Chia, Y.C., Wan Sulaiman, W.A., Suppiah, S., Mohamed, M.H., and Veettil, S.K. (2018). Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth 18, 494.

Lillycrop, K.A., Garratt, E.S., Titcombe, P., Melton, P.E., Murray, R.J.S., Barton, S.J., Clarke-Harris, R., Costello, P.M., Holbrook, J.D., Hopkins, J.C., et al. (2019). Differential SLC6A4 methylation: a predictive epigenetic marker of adiposity from birth to adulthood. Int. J. Obes. 43, 974–988.

Linné, Y., Dye, L., Barkeling, B., and Rössner, S. (2004). Long-Term Weight Development in Women: A 15-Year Follow-up of the Effects of Pregnancy. Obes. Res. 12, 1166–1178.

Llewellyn, C.H., van Jaarsveld, C.H.M., Johnson, L., Carnell, S., and Wardle, J. (2011). Development and factor structure of the Baby Eating Behaviour Questionnaire in the Gemini birth cohort. Appetite 57, 388–396.

Lobstein, T., and Millstone, E. (2007). Context for the PorGrow study: Europe's obesity crisis. Obes. Rev. 8, 7–16.

Lobstein, T., Jackson-Leach, R., Moodie, M.L., Hall, K.D., Gortmaker, S.L., Swinburn, B.A., James, W.P.T., Wang, Y., and McPherson, K. (2015). Child and adolescent obesity: part of a bigger picture. Lancet Lond. Engl. 385, 2510–2520.

Long, N.M., Nathanielsz, P.W., and Ford, S.P. (2012). The impact of maternal overnutrition and obesity on hypothalamic-pituitary-adrenal axis, response of offspring to stress. Domest. Anim. Endocrinol. 42, 195–202.

Long, N.M., Rule, D.C., Tuersunjiang, N., Nathanielsz, P.W., and Ford, S.P. (2015). Maternal Obesity in Sheep Increases Fatty Acid Synthesis, Upregulates Nutrient Transporters, and Increases Adiposity in Adult Male Offspring after a Feeding Challenge. PLoS ONE 10.

Longo, M., Zatterale, F., Naderi, J., Parrillo, L., Formisano, P., Raciti, G.A., Beguinot, F., and Miele, C. (2019). Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int. J. Mol. Sci. 20.

Lotta, L.A., Mokrosiński, J., Mendes de Oliveira, E., Li, C., Sharp, S.J., Luan, J., Brouwers, B., Ayinampudi, V., Bowker, N., Kerrison, N., et al. (2019). Human Gain-of-Function MC4R Variants Show Signaling Bias and Protect against Obesity. Cell 177, 597–607.e9.

Luoto, R., Kinnunen, T.I., Aittasalo, M., Kolu, P., Raitanen, J., Ojala, K., Mansikkamäki, K., Lamberg, S., Vasankari, T., and Komulainen, T. (2011). Primary prevention of gestational diabetes mellitus and large-for-gestational-age newborns by lifestyle counseling: a cluster-randomized controlled trial. PLoS Med. 8, e1001036.

Mackenbach, J.D., Rutter, H., Compernolle, S., Glonti, K., Oppert, J.-M., Charreire, H., De Bourdeaudhuij, I., Brug, J., Nijpels, G., and Lakerveld, J. (2014). Obesogenic environments: a systematic review of the association between the physical environment and adult weight status, the SPOTLIGHT project. BMC Public Health 14, 233.

Magno, F.C.C.M., Guaraná, H.C., Fonseca, A.C.P., Cabello, G.M.K., Carneiro, J.R.I., Pedrosa, A.P., Ximenes, A.C., and Rosado, E.L. (2018). Influence of FTO rs9939609 polymorphism on appetite, ghrelin, leptin, IL6, TNFα levels, and food intake of women with morbid obesity. Diabetes Metab. Syndr. Obes. Targets Ther. 11, 199–207.

Martin, A., Booth, J.N., McGeown, S., Niven, A., Sproule, J., Saunders, D.H., and Reilly, J.J. (2017). Longitudinal Associations Between Childhood Obesity and Academic Achievement: Systematic Review with Focus Group Data. Curr. Obes. Rep. 6, 297–313.

Martin, R.M., Patel, R., Kramer, M.S., Guthrie, L., Vilchuck, K., Bogdanovich, N., Sergeichick, N., Gusina, N., Foo, Y., Palmer, T., et al. (2013). Effects of promoting increased duration and

exclusivity of breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial. JAMA J. Am. Med. Assoc. 309, 1005–1013.

Martínez, M.E., Marshall, J.R., and Sechrest, L. (1998). Invited commentary: Factor analysis and the search for objectivity. Am. J. Epidemiol. 148, 17–19.

Martin-Rodriguez, E., Guillen-Grima, F., Martí, A., and Brugos-Larumbe, A. (2015). Comorbidity associated with obesity in a large population: The APNA study. Obes. Res. Clin. Pract. 9, 435–447.

Martins, E.B., and Carvalho, M.S. (2006). Birth weight and overweight in childhood: a systematic review. Cad. Saude Publica 22, 2281–2300.

Marvin-Dowle, K., Kilner, K., Burley, V., and Soltani, H. (2018). Differences in dietary pattern by maternal age in the Born in Bradford cohort: A comparative analysis. PLOS ONE 13, e0208879.

Mazzocchi, A., Giannì, M.L., Morniroli, D., Leone, L., Roggero, P., Agostoni, C., De Cosmi, V., and Mosca, F. (2019). Hormones in Breast Milk and Effect on Infants' Growth: A Systematic Review. Nutrients 11.

McAndrew, F., Thompson, J., Fellows, L., Large, A., Speed, M., and Renfrew, M.J. (2012). Infant feeding survey 2010. Leeds Health Soc. Care Inf. Cent.

McCance, R.A., and Widdowson, E.. (2015). McCance and Widdowson's the composition of foods (Public Health England, & Royal Society of Chemistry).

McCarthy, E.K., Chaoimh, C. ní, Murray, D.M., Hourihane, J.O., Kenny, L.C., and Kiely, M. (2015a). Eating behaviour and weight status at 2 years of age: data from the Cork BASELINE Birth Cohort Study. Eur. J. Clin. Nutr. 69, 1356–1359.

McCarthy, E.K., Chaoimh, C. ní, Murray, D.M., Hourihane, J.O. 'B, Kenny, L.C., and Kiely, M. (2015b). Eating behaviour and weight status at 2 years of age: data from the Cork BASELINE Birth Cohort Study. Eur. J. Clin. Nutr. 69, 1356–1359.

Mensink, M., Feskens, E.J., Kruijshoop, M., de Bruin, T.W., Saris, W.H., and Blaak, E.E. (2003). Subscapular skinfold thickness distinguishes between transient and persistent impaired glucose tolerance: Study on Lifestyle-Intervention and Impaired Glucose Tolerance Maastricht (SLIM). Diabet. Med. 20, 552–557.

Menting, M.D., Mintjens, S., Beek, C., Frick, C.J., Ozanne, S.E., Limpens, J., Roseboom, T.J., Hooijmans, C.R., Deutekom, A.W., and Painter, R.C. (2019). Maternal obesity in pregnancy impacts offspring cardiometabolic health: Systematic review and meta-analysis of animal studies. Obes. Rev. 20, 675–685.

Metzger, B.E., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustan, D.R., Hadden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J.N., et al. (2008). HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N. Engl. J. Med. 358, 1991–2002.

Mikkilä, V., Räsänen, L., Raitakari, O.T., Pietinen, P., and Viikari, J. (2005). Consistent dietary patterns identified from childhood to adulthood: the cardiovascular risk in Young Finns Study. Br. J. Nutr. 93, 923–931.

Miller, A.L., Lumeng, J.C., and LeBourgeois, M.K. (2015). Sleep patterns and obesity in childhood. Curr. Opin. Endocrinol. Diabetes Obes. 22, 41.

Mills, H.L., Patel, N., White, S.L., Pasupathy, D., Briley, A.L., Santos Ferreira, D.L., Seed, P.T., Nelson, S.M., Sattar, N., Tilling, K., et al. (2019). The effect of a lifestyle intervention in obese pregnant women on gestational metabolic profiles: findings from the UK Pregnancies Better Eating and Activity Trial (UPBEAT) randomised controlled trial. BMC Med. 17, 15.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.

Molle, R.D., Bischoff, A.R., Portella, A.K., and Silveira, P.P. (2016). The fetal programming of food preferences: current clinical and experimental evidence. J. Dev. Orig. Health Dis. 7, 222–230.

Molyneaux, E., Poston, L., Khondoker, M., and Howard, L.M. (2016). Obesity, antenatal depression, diet and gestational weight gain in a population cohort study. Arch. Womens Ment. Health 19, 899–907.

More, J., and Emmett, P. (2015). Evidenced-based, practical food portion sizes for preschool children and how they fit into a well balanced, nutritionally adequate diet. J. Hum. Nutr. Diet. 28, 135–154.

Mustila, T., Raitanen, J., Keskinen, P., Saari, A., and Luoto, R. (2012). Lifestyle counselling during pregnancy and offspring weight development until four years of age: Follow-up study of a controlled trial. J. Negat. Results Biomed. 11, 11.

Nanchen, D., Locatelli, I., Cornuz, J., Kors, J.A., Jan, H., Deckers, J.W., Hofman, A., Franco, O.., Stricker, B.., Witteman, J.C.., et al. (2013). Resting Heart Rate and the Risk of Heart Failure in Healthy Adults. Circ. Heart Fail. 6, 403–410.

Nathanielsz, P.W., Yan, J., Green, R., Nijland, M., Miller, J.W., Wu, G., McDonald, T.J., and Caudill, M.A. (2015). Maternal obesity disrupts the methionine cycle in baboon pregnancy. Physiol. Rep. 3.

National Obesity Observatory (2010). Adult Obesity and Socioeconomic status.

Neelon, S.E.B., Andersen, C.S., Morgen, C.S., Kamper-Jørgensen, M., Oken, E., Gillman, M.W., and Sørensen, T.I.A. (2015). Early child care and obesity at 12 months of age in the Danish National Birth Cohort. Int. J. Obes. 39, 33–38.

Nelson, S.M., Matthews, P., and Poston, L. (2010). Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. Hum. Reprod. Update 16, 255–275.

NHS (2010). Health Survey for England.

NHS (2015). National Child Measurement Programme.

NHS (2018). Statistics on Obesity, Physical Activity and Diet.

NICE (2010). Weight management before, during and after pregnancy (PH27).

NICE (2014). Obesity: identification, assessment and management (CG189).

Nicklaus, S., Boggio, V., Chabanet, C., and Issanchou, S. (2005). A prospective study of food variety seeking in childhood, adolescence and early adult life. Appetite 44, 289–297.

Nigatu, Y.T., Reijneveld, S.A., de Jonge, P., van Rossum, E., and Bültmann, U. (2016). The Combined Effects of Obesity, Abdominal Obesity and Major Depression/Anxiety on Health-Related Quality of Life: the LifeLines Cohort Study. PLoS ONE 11.

North, K., and Emmett, P. (2000). Multivariate analysis of diet among three-year-old children and associations with socio-demographic characteristics. The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) Study Team. Eur. J. Clin. Nutr. 54, 73–80.

Northstone, K., and Emmett, P.M. (2008). Are dietary patterns stable throughout early and mid-childhood? A birth cohort study. Br. J. Nutr. 100, 1069–1076.

O'Brien, O., McCarthy, M., Gibney, E., and McAuliffe, F. (2014). Technology-supported dietary and lifestyle interventions in healthy pregnant women: a systematic review. Eur. J. Clin. Nutr. 68, 760–766.

Oikonomou, E.K., and Antoniades, C. (2019). The role of adipose tissue in cardiovascular health and disease. Nat. Rev. Cardiol. 16, 83–99.

Oken, E., Levitan, E., and Gillman, M. (2008). Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. Int. J. Obes. 32, 201.

Okubo, H., Crozier, S.R., Harvey, N.C., Godfrey, K.M., Inskip, H.M., Cooper, C., and Robinson, S.M. (2014). Maternal dietary glycemic index and glycemic load in early pregnancy are associated with offspring adiposity in childhood: the Southampton Women's Survey. Am. J. Clin. Nutr. 100, 676–683.

Okubo, H., Crozier, S.R., Harvey, N.C., Godfrey, K.M., Inskip, H.M., Cooper, C., and Robinson, S.M. (2015). Diet quality across early childhood and adiposity at 6 years: the Southampton Women's Survey. Int. J. Obes. 39, 1456–1462.

Oliveira, A., de Lauzon-Guillain, B., Jones, L., Emmett, P., Moreira, P., Ramos, E., Charles, M.A., and Lopes, C. (2015). Birth weight and eating behaviors of young children. J. Pediatr. 166, 59–65.

de Onis, M. (2006). Child Growth Standards based on length/height, weight and age. Acta Paediatr. 95, 76–85.

Oteng-Ntim, E., Varma, R., Croker, H., Poston, L., and Doyle, P. (2012). Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Med. 10, 47.

Owen, C.G., Whincup, P.H., Orfei, L., Chou, Q.-A., Rudnicka, A.R., Wathern, A.K., Kaye, S.J., Eriksson, J.G., Osmond, C., and Cook, D.G. (2009). Is body mass index before middle age related to coronary heart disease risk in later life? Evidence from observational studies. Int. J. Obes. 2005 33, 866–877.

Page, K.A., Luo, S., Wang, X., Chow, T., Alves, J., Buchanan, T.A., and Xiang, A.H. (2019). Children Exposed to Maternal Obesity or Gestational Diabetes During Early Fetal Development Have Hypothalamic Alterations That Predict Future Weight Gain. Diabetes Care.

Painter, R.C., Roseboom, T.J., and Bleker, O.P. (2005). Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod. Toxicol. 20, 345–352.

Patel, N., Pasupathy, D., and Poston, L. (2015). Determining the consequences of maternal obesity for offspring health. Exp. Physiol. 100, 1421–1428.

Patel, N., Godfrey, K., Pasupathy, D., Levin, J., Flynn, A., Hayes, L., Briley, A., Bell, R., Lawlor, D., and Oteng-Ntim, E. (2017a). Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy. Int. J. Obes. 41, 1018–1026.

Patel, N., Hellmuth, C., Uhl, O., Godfrey, K., Briley, A., Welsh, P., Pasupathy, D., Seed, P.T., Koletzko, B., and Poston, L. (2017b). Cord Metabolic Profiles in Obese Pregnant Women: Insights Into Offspring Growth and Body Composition. J. Clin. Endocrinol. Metab. 103, 346–355.

Patel, N., Dalrymple, K.V., Briley, A.L., Pasupathy, D., Seed, P.T., Flynn, A.C., Poston, L., and on behalf of the UPBEAT Consortium (2018). Mode of infant feeding, eating behaviour and anthropometry in infants at 6-months of age born to obese women – a secondary analysis of the UPBEAT trial. BMC Pregnancy Childbirth 18, 355.

Patel, R., Lawlor, D.A., Kramer, M.S., Smith, G.D., Bogdanovich, N., Matush, L., and Martin, R.M. (2011). Socio-economic position and adiposity among children and their parents in the Republic of Belarus. Eur. J. Public Health 21, 158–165.

Pei, Z., Flexeder, C., Fuertes, E., Standl, M., Berdel, D., von Berg, A., Koletzko, S., Schaaf, B., and Heinrich, J. (2014). Mother's body mass index and food intake in school-aged children: results of the GINIplus and the LISAplus studies. Eur. J. Clin. Nutr. 68, 898–906.

Penfold, N.C., and Ozanne, S.E. (2015). Developmental programming by maternal obesity in 2015: Outcomes, mechanisms, and potential interventions. Horm. Behav. 76, 143–152.

Perng, W., Gillman, M.W., Mantzoros, C.S., and Oken, E. (2014). A prospective study of maternal prenatal weight and offspring cardiometabolic health in midchildhood. Ann. Epidemiol. 24, 793–800.e1.

Phelan, S. (2010). Pregnancy: a "teachable moment" for weight control and obesity prevention. Am. J. Obstet. Gynecol. 202, 135.e1-135.e8.

van der Pligt, P., Willcox, J., Hesketh, K.D., Ball, K., Wilkinson, S., Crawford, D., and Campbell, K. (2013). Systematic review of lifestyle interventions to limit postpartum weight retention: implications for future opportunities to prevent maternal overweight and obesity following childbirth. Obes Rev 14, 792–805.

Plows, J.F., Stanley, J.L., Baker, P.N., Reynolds, C.M., and Vickers, M.H. (2018). The Pathophysiology of Gestational Diabetes Mellitus. Int. J. Mol. Sci. 19, 3342.

Poston, L. (2010). Developmental programming and diabetes - The human experience and insight from animal models. Best Pract. Res. Clin. Endocrinol. Metab. 24, 541–552.

Poston, L. (2012). Maternal obesity, gestational weight gain and diet as determinants of offspring long term health. Best Pract. Res. Clin. Endocrinol. Metab. 26, 627–639.

Poston, L., Harthoorn, L.F., and Beek, E.M. van der (2011). Obesity in Pregnancy: Implications for the Mother and Lifelong Health of the Child. A Consensus Statement. Pediatr. Res. 69, 175–180.

Poston, L., Briley, A.L., Barr, S., Bell, R., Croker, H., Coxon, K., Essex, H.N., Hunt, C., Hayes, L., Howard, L.M., et al. (2013). Developing a complex intervention for diet and activity behaviour change in obese pregnant women (the UPBEAT trial); assessment of behavioural change and process evaluation in a pilot randomised controlled trial. BMC Pregnancy Childbirth 13, 148.
Poston, L., Bell, R., Croker, H., Flynn, A.C., Godfrey, K.M., Goff, L., Hayes, L., Khazaezadeh, N., Nelson, S.M., and Oteng-Ntim, E. (2015). Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 3, 767–777.

Poston, L., Caleyachetty, R., Cnattingius, S., Corvalán, C., Uauy, R., Herring, S., and Gillman, M.W. (2016). Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol. 4, 1025–1036.

Public Health England (2020). NCMP and Child Obesity Profile: short statistical commentary March 2020.

Ramamoorthy, T.G., Allen, T.-J., Davies, A., Harno, E., Sefton, C., Murgatroyd, C., and White, A. (2018). Maternal overnutrition programs epigenetic changes in the regulatory regions of hypothalamic Pomc in the offspring of rats. Int. J. Obes. 42, 1431–1444.

Rao, K.R., Padmavathi, I.J.N., and Raghunath, M. (2012). Maternal micronutrient restriction programs the body adiposity, adipocyte function and lipid metabolism in offspring: A review. Rev. Endocr. Metab. Disord. 13, 103–108.

Rasmussen, K.M., Catalano, P.M., and Yaktine, A.L. (2009). New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. Curr. Opin. Obstet. Gynecol. 21, 521–526.

Rauh, K., Gabriel, E., Kerschbaum, E., Schuster, T., von Kries, R., Amann-Gassner, U., and Hauner, H. (2013). Safety and efficacy of a lifestyle intervention for pregnant women to prevent excessive maternal weight gain: a cluster-randomized controlled trial. BMC Pregnancy Childbirth 13, 151.

Rauh, K., Gunther, J., Kunath, J., Stecher, L., and Hauner, H. (2015). Lifestyle intervention to prevent excessive maternal weight gain: Mother and infant follow-up at 12 months postpartum. BMC Pregnancy Childbirth 15 (1).

RCOG (2018). NMPA Project Team. National Maternity and Perinatal Audit: Clinical Report 2017. (London).

Reilly, J.J., Methven, E., McDowell, Z.C., Hacking, B., Alexander, D., Stewart, L., and Kelnar, C.J.H. (2003). Health consequences of obesity. Arch. Dis. Child. 88, 748–752.

Reilly, J.J., Armstrong, J., Dorosty, A.R., Emmett, P.M., Ness, A., Rogers, I., Steer, C., and Sherriff, A. (2005). Early life risk factors for obesity in childhood: cohort study. BMJ 330, 1357.
Reinehr, T., Hetherington, M., Nekitsing, C., McNally, J., Shloim, N., and Ekelund, U. (2017). Aetiology of obesity in children. In Advanced Nutrition and Dietetics in Obesity, (John Wiley & Sons, Ltd), pp. 261–286.

Renault, K.M., Norgaard, K., Nilas, L., Carlsen, E.M., Cortes, D., Pryds, O., and Secher, N.J. (2014). The Treatment of Obese Pregnant Women (TOP) study: A randomized controlled trial of the effect of physical activity intervention assessed by pedometer with or without dietary intervention in obese pregnant women. Am. J. Obstet. Gynecol. 210, 134.e1-134.e9.

Reynolds, C.M., Segovia, S.A., and Vickers, M.H. (2017). Experimental Models of Maternal Obesity and Neuroendocrine Programming of Metabolic Disorders in Offspring. Front. Endocrinol. 8.

Reynolds, C.M.E., Egan, B., O'Malley, E.G., McMahon, L., Sheehan, S.R., and Turner, M.J. (2020). Longitudinal Study of Maternal BMI in Successive Pregnancies. Obesity 28, 460–467.

Reynolds, R.M., Allan, K.M., Raja, E.., Bhattacharya, S., McNeill, G., Hannaford, P.C., Sarwar, N., Lee, A.J., Bhattacharya, S., and Norman, J.E. (2013). Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ 347, f4539.

Richmond, R.C., Al-Amin, A., Smith, G.D., and Relton, C.L. (2014). Approaches for drawing causal inferences from epidemiological birth cohorts: a review. Early Hum. Dev. 90, 769–780.
Richmond, R.C., Timpson, N.J., Felix, J.F., Palmer, T., Gaillard, R., McMahon, G., Smith, G.D., Jaddoe, V.W., and Lawlor, D.A. (2017). Using genetic variation to explore the causal effect of maternal pregnancy adiposity on future offspring adiposity: a Mendelian randomisation study. PLoS Med. 14, e1002221.

Rito, A.I., Buoncristiano, M., Spinelli, A., Salanave, B., Kunešová, M., Hejgaard, T., García Solano, M., Fijałkowska, A., Sturua, L., Hyska, J., et al. (2019). Association between Characteristics at Birth, Breastfeeding and Obesity in 22 Countries: The WHO European Childhood Obesity Surveillance Initiative – COSI 2015/2017. Obes. Facts 12, 226–243.

Riveros-McKay, F., Mistry, V., Bounds, R., Hendricks, A., Keogh, J.M., Thomas, H., Henning, E., Corbin, L.J., Understanding Society Scientific Group, O'Rahilly, S., et al. (2019). Genetic architecture of human thinness compared to severe obesity. PLoS Genet. 15, e1007603.

Roberto, C.A., Swinburn, B., Hawkes, C., Huang, T.T.-K., Costa, S.A., Ashe, M., Zwicker, L., Cawley, J.H., and Brownell, K.D. (2015). Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. The Lancet 385, 2400–2409.

Roberts, V.H.J., Frias, A.E., and Grove, K.L. (2015). Impact of Maternal Obesity on Fetal Programming of Cardiovascular Disease. Physiology 30, 224–231.

Robinson, S., Marriott, L., Poole, J., Crozier, S., Borland, S., Lawrence, W., Law, C., Godfrey, K., Cooper, C., Inskip, H., et al. (2007). Dietary patterns in infancy: the importance of maternal and family influences on feeding practice. Br. J. Nutr. 98, 1029–1037.

Robinson, S.M., Crozier, S.R., Harvey, N.C., Barton, B.D., Law, C.M., Godfrey, K.M., Cooper, C., and Inskip, H.M. (2015). Modifiable early-life risk factors for childhood adiposity and overweight: an analysis of their combined impact and potential for prevention. Am. J. Clin. Nutr. 101, 368–375.

Rogers, I., Emmett, P., and ALSPAC Study Team (2003). The effect of maternal smoking status, educational level and age on food and nutrient intakes in preschool children: results from the Avon Longitudinal Study of Parents and Children. Eur. J. Clin. Nutr. 57, 854–864.

Rohde, K., Keller, M., la Cour Poulsen, L., Blüher, M., Kovacs, P., and Böttcher, Y. (2019). Genetics and epigenetics in obesity. Metabolism 92, 37–50.

Rolland-Cachera, M.F., Deheeger, M., Bellisle, F., Sempé, M., Guilloud-Bataille, M., and Patois, E. (1984). Adiposity rebound in children: a simple indicator for predicting obesity. Am. J. Clin. Nutr. 39, 129–135.

Rollins, B.Y., Loken, E., Savage, J.S., and Birch, L.L. (2014). Maternal controlling feeding practices and girls' inhibitory control interact to predict changes in BMI and eating in the absence of hunger from 5 to 7 y. Am. J. Clin. Nutr. 99, 249–257.

Romero-Corral, A., Somers, V.K., Sierra-Johnson, J., Thomas, R.J., Collazo-Clavell, M.L., Korinek, J., Allison, T.G., Batsis, J.A., Sert-Kuniyoshi, F.H., and Lopez-Jimenez, F. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. Int. J. Obes. 32, 959–966.

Ronnberg, A., Ostlund, I., Fadl, H., Gottvall, T., and Nilsson, K. (2015). Intervention during pregnancy to reduce excessive gestational weight gain—a randomised controlled trial. BJOG Int. J. Obstet. Gynaecol. 122, 537–544.

Ronnberg, A., Hanson, U., and Nilsson, K. (2017). Effects of an antenatal lifestyle intervention on offspring obesity–a five year follow-up of a randomised controlled trial. Acta Obstet. Gynecol. Scand. 96, 1093–1099.

Roseboom, T.J., Van Der Meulen, J.H., Ravelli, A.C., Osmond, C., Barker, D.J., and Bleker, O.P. (2001). Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Mol. Cell. Endocrinol. 185, 93–98.

Rossi, C.E., and Vasconcelos, F. de A.G. de (2010). Birth weight and obesity in children and adolescents: a systematic review. Rev. Bras. Epidemiol. 13, 246–258.

Ruchat, S.-M., Houde, A.-A., Voisin, G., St-Pierre, J., Perron, P., Baillargeon, J.-P., Gaudet, D., Hivert, M.-F., Brisson, D., and Bouchard, L. (2013). Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics 8, 935–943.

Saari, A., Sankilampi, U., Hannila, M.-L., Kiviniemi, V., Kesseli, K., and Dunkel, L. (2011). New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. Ann. Med. 43, 235–248.

Sadeh, A. (2004). A brief screening questionnaire for infant sleep problems: validation and findings for an Internet sample. Pediatrics 113, e570-577.

Samuelsson, A.-M., Matthews, P.A., Argenton, M., Christie, M.R., McConnell, J.M., Jansen, E.H., Piersma, A.H., Ozanne, S.E., Twinn, D.F., and Remacle, C. (2008). Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance. Hypertension 51, 383–392.

Samuelsson, A.-M., Morris, A., Igosheva, N., Kirk, S.L., Pombo, J.M., Coen, C.W., Poston, L., and Taylor, P.D. (2010). Evidence for sympathetic origins of hypertension in juvenile offspring of obese rats. Hypertension 55, 76–82.

Samuelsson, A.-M., Clark, J., Rudyk, O., Shattock, M.J., Bae, S.E., South, T., Pombo, J., Redington, K., Uppal, E., and Coen, C.W. (2013). Experimental Hyperleptinemia in Neonatal

Rats Leads to Selective Leptin Responsiveness, Hypertension, and Altered Myocardial FunctionNovelty and Significance. Hypertension 62, 627–633.

Samura, T., Steer, J., Michelis, L.D., Carroll, L., Holland, E., and Perkins, R. (2016). Factors Associated With Excessive Gestational Weight Gain: Review of Current Literature. Glob. Adv. Health Med. 5, 87–93.

Santos, S., Gaillard, R., Oliveira, A., Barros, H., Hofman, A., Franco, O.H., and Jaddoe, V.W. (2016). Subcutaneous fat mass in infancy and cardiovascular risk factors at school-age: The generation R study. Obesity 24, 424–429.

Sarantopoulos, C.N., Banyard, D.A., Ziegler, M.E., Sun, B., Shaterian, A., and Widgerow, A.D. (2018). Elucidating the Preadipocyte and Its Role in Adipocyte Formation: a Comprehensive Review. Stem Cell Rev. Rep. 14, 27–42.

Scaglioni, S., De Cosmi, V., Ciappolino, V., Parazzini, F., Brambilla, P., and Agostoni, C. (2018). Factors Influencing Children's Eating Behaviours. Nutrients 10, 706.

Scharf, R.J., and DeBoer, M.D. (2016). Sugar-Sweetened Beverages and Children's Health. Annu. Rev. Public Health 37, 273–293.

Schwartz, C., Scholtens, P.A.M.J., Lalanne, A., Weenen, H., and Nicklaus, S. (2011). Development of healthy eating habits early in life. Review of recent evidence and selected guidelines. Appetite 57, 796–807.

Simmonds, M., Llewellyn, A., Owen, C., and Woolacott, N. (2016). Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes. Rev. 17, 95–107.

Singh, A.S., Mulder, C., Twisk, J.W., Van Mechelen, W., and Chinapaw, M.J. (2008). Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes. Rev. 9, 474–488.

Skinner, J.D., Carruth, B.R., Bounds, W., Ziegler, P., and Reidy, K. (2002). Do food-related experiences in the first 2 years of life predict dietary variety in school-aged children? J. Nutr. Educ. Behav. 34, 310–315.

Sleddens, E.F., Kremers, S.P., and Thijs, C. (2008). The children's eating behaviour questionnaire: factorial validity and association with Body Mass Index in Dutch children aged 6-7. Int. J. Behav. Nutr. Phys. Act. 5, 49.

Smith, J., Cianflone, K., Biron, S., Hould, F., Lebel, S., Marceau, S., Lescelleur, O., Biertho, L., Simard, S., and Kral, J. (2009). Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. J. Clin. Endocrinol. Metab. 94, 4275–4283.

Snijder, M.B., van Dam, R.M., Visser, M., and Seidell, J.C. (2006). What aspects of body fat are particularly hazardous and how do we measure them? Int. J. Epidemiol. 35, 83–92.

Sonntag, D., Ali, S., and Bock, F.D. (2016). Lifetime indirect cost of childhood overweight and obesity: A decision analytic model. Obesity 24, 200–206.

Spalding, K.L., Arner, E., Westermark, P.O., Bernard, S., Buchholz, B.A., Bergmann, O., Blomqvist, L., Hoffstedt, J., Näslund, E., Britton, T., et al. (2008). Dynamics of fat cell turnover in humans. Nature 453, 783–787.

Speiser, P.W., Rudolf, M.C., Anhalt, H., Camacho-Hubner, C., Chiarelli, F., Eliakim, A., Freemark, M., Gruters, A., Hershkovitz, E., and Iughetti, L. (2005). Childhood obesity. J. Clin. Endocrinol. Metab. 90, 1871–1887.

Spence, J.C., Carson, V., Casey, L., and Boule, N. (2011). Examining behavioural susceptibility to obesity among Canadian pre-school children: the role of eating behaviours. Int. J. Pediatr. Obes. IJPO Off. J. Int. Assoc. Study Obes. 6, e501-507.

Squires, J., and Bricker, D. (2009). Ages & Stages Questionnaires[R], Third Edition (ASQ-3[TM]): A Parent-Completed Child-Monitoring System (Brookes Publishing Company).

Srinivasan, S.R., Frontini, M.G., and Berenson, G.S. (2003). Longitudinal changes in risk variables of insulin resistance syndrome from childhood to young adulthood in offspring of parents with type 2 diabetes: the Bogalusa Heart Study. Metabolism 52, 443–450.

Stephenson, J., Heslehurst, N., Hall, J., Schoenaker, D.A.J.M., Hutchinson, J., Cade, J.E., Poston, L., Barrett, G., Crozier, S.R., Barker, M., et al. (2018). Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. Lancet Lond. Engl. 391, 1830–1841.

Strong, W.B., Malina, R.M., Blimkie, C.J.R., Daniels, S.R., Dishman, R.K., Gutin, B., Hergenroeder, A.C., Must, A., Nixon, P.A., Pivarnik, J.M., et al. (2005). Evidence Based Physical Activity for School-age Youth. J. Pediatr. 146, 732–737.

Sumithran, P., Houlihan, C., Shub, A., Churilov, L., Pritchard, N., Price, S., Ekinci, E., Proietto, J., and Permezel, M. (2018). How common is substantial weight gain after pregnancy? Obes. Res. Clin. Pract. 12, 139–145.

Symonds, M.E., Pope, M., Sharkey, D., and Budge, H. (2012). Adipose tissue and fetal programming. Diabetologia 55, 1597–1606.

Taal, H.R., vd Heijden, A.J., Steegers, E.A.P., Hofman, A., and Jaddoe, V.W.V. (2013). Small and large size for gestational age at birth, infant growth, and childhood overweight. Obesity 21, 1261–1268.

Tam, C.H.T., Ma, R.C.W., Yuen, L.Y., Ozaki, R., Li, A.M., Hou, Y., Chan, M.H.M., Ho, C.S., Yang, X., Chan, J.C.N., et al. (2018). The impact of maternal gestational weight gain on cardiometabolic risk factors in children. Diabetologia 61, 2539–2548.

Tanvig, M., Vinter, C.A., Jorgensen, J.S., Wehberg, S., Ovesen, P.G., Lamont, R.F., Beck-Nielsen, H., Christesen, H.T., and Jensen, D.M. (2014). Anthropometrics and body composition by dual energy x-ray in children of obese women: A follow-up of a randomized controlled trial (the Lifestyle in Pregnancy and Offspring [LiPO] study). PLoS ONE 9, e89590.

Taylor, P.D., and Poston, L. (2007). Developmental programming of obesity in mammals. Exp. Physiol. 92, 287–298.

Taylor, P.D., Samuelsson, A.-M., and Poston, L. (2014). Maternal obesity and the developmental programming of hypertension: a role for leptin. Acta Physiol. 210, 508–523.

Temple, J.L., Cordero, P., Li, J., Nguyen, V., and Oben, J.A. (2016). A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence. Int. J. Mol. Sci. 17, 947.

Tessier, D., Ferraro, Z., and Gruslin, A. (2013). Role of leptin in pregnancy: consequences of maternal obesity. Placenta 34, 205–211.

Thangaratinam, S., Rogozińska, E., Jolly, K., Glinkowski, S., Roseboom, T., Tomlinson, J., Kunz, R., Mol, B., Coomarasamy, A., and Khan, K. (2012). Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. Br. Med. J. 344, e2088.

The IPAQ Group (2005). Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms Contents.

Thomson, J.L., Tussing-Humphreys, L.M., and Goodman, M.H. (2014). Delta Healthy Sprouts: a randomized comparative effectiveness trial to promote maternal weight control and reduce childhood obesity in the Mississippi Delta. Contemp. Clin. Trials 38, 82–91.

Thornburg, K.L. (2015). The programming of cardiovascular disease. J. Dev. Orig. Health Dis. 6, 366–376.

Tremblay, M.S., and Willms, J.D. (2003). Is the Canadian childhood obesity epidemic related to physical inactivity? Int. J. Obes. 27, 1100–1105.

Tremblay, M.S., Gray, C.E., Akinroye, K., Harrington, D.M., Katzmarzyk, P.T., Lambert, E.V., Liukkonen, J., Maddison, R., Ocansey, R.T., and Onywera, V.O. (2014). Physical activity of children: a global matrix of grades comparing 15 countries. J. Phys. Act. Health 11, S113–S125.

UK Government: Department of Health and Social Care (2018). Childhood obesity: a plan for action.

UNESCO (2016). Early Childhood Care and Education.

UNFPA (2016). Sexual and reproductive health.

Vesco, K.K., Karanja, N., King, J.C., Gillman, M.W., Leo, M.C., Perrin, N., McEvoy, C.T., Eckhardt, C.L., Smith, K.S., and Stevens, V.J. (2014). Efficacy of a group-based dietary intervention for limiting gestational weight gain among obese women: A randomized trial. Obesity 22, 1989–1996.

Vesco, K.K., Leo, M.C., Karanja, N., Gillman, M.W., McEvoy, C.T., King, J.C., Eckhardt, C.L., Smith, K.S., Perrin, N., and Stevens, V.J. (2016). One-year postpartum outcomes following a weight management intervention in pregnant women with obesity. Obesity 24, 2042–2049.

Viana, V., Sinde, S., and Saxton, J.C. (2008). Children's Eating Behaviour Questionnaire: associations with BMI in Portuguese children. Br. J. Nutr. 100, 445–450.

Vickers, M.., and Sloboda, D.. (2012). Leptin as mediator of the effects of developmental programming. Best Pract. Res. Clin. Endocrinol. Metab. 26, 677–687.

Victora, C.G., Bahl, R., Barros, A.J., França, G.V., Horton, S., Krasevec, J., Murch, S., Sankar, M.J., Walker, N., and Rollins, N.C. (2016). Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. The Lancet 387, 475–490.

Vinter, C.A., Jensen, D.M., Ovesen, P., Beck-Nielsen, H., and Jorgensen, J.S. (2011). The LiP (Lifestyle in Pregnancy) study: A randomized controlled trial of lifestyle intervention in 360 obese pregnant women. Diabetes Care 34, 2502–2507.

Voerman, E., Santos, S., Golab, B., and Amiano, B. (2019). Maternal body mass index, gestational weight gain and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. PLOS Med. In Press.

Voors, A., Webber, L., and Berenson, G. (1982). Resting heart rate and pressure-rate product of children in a total biracial community: the Bogalusa Heart Study. Am. J. Epidemiol. 116, 276–286.

Wadden, T., and Bray, G. (2018). Handbook of Obesity Treatment.

Walsh, J.M., McGowan, C.A., Mahony, R., Foley, M.E., and McAuliffe, F.M. (2012). Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. Br. Med. J. 345, e5605.

Ward, Z.J., Long, M.W., Resch, S.C., Giles, C.M., Cradock, A.L., and Gortmaker, S.L. (2017). Simulation of Growth Trajectories of Childhood Obesity into Adulthood. N. Engl. J. Med. 377, 2145–2153.

Wardle, J., Guthrie, C.A., Sanderson, S., and Rapoport, L. (2001). Development of the Children's Eating Behaviour Questionnaire. J Child Psychol Psychiatry 42, 963–970.

Webb, T.L., Sniehotta, F.F., and Michie, S. (2010). Using theories of behaviour change to inform interventions for addictive behaviours. Addict. Abingdon Engl. 105, 1879–1892.

Webber, L., Hill, C., Saxton, J., Jaarsveld, C.H.M.V., and Wardle, J. (2009). Eating behaviour and weight in children. Int. J. Obes. 33, 21–28.

Webber, L., Divajeva, D., Marsh, T., McPherson, K., Brown, M., Galea, G., and Breda, J. (2014). The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. BMJ Open 4, e004787.

Wellings, K., Jones, K.G., Mercer, C.H., Tanton, C., Clifton, S., Datta, J., Copas, A.J., Erens, B., Gibson, L.J., and Macdowall, W. (2013). The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). The Lancet 382, 1807–1816.

Whitaker, R.C., Pepe, M.S., Wright, J.A., Seidel, K.D., and Dietz, W.H. (1998). Early adiposity rebound and the risk of adult obesity. Pediatrics 101, E5.

White, I.R., Horton, N.J., Carpenter, J., Statistics, R. in M. and S., and Pocock, S.J. (2011). Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 342, d40.

Wolters, M., Joslowski, G., Plachta-Danielzik, S., Standl, M., Müller, M.J., Ahrens, W., and Buyken, A.E. (2018). Dietary Patterns in Primary School are of Prospective Relevance for the Development of Body Composition in Two German Pediatric Populations. Nutrients 10.

Woo Baidal, J.A., Locks, L.M., Cheng, E.R., Blake-Lamb, T.L., Perkins, M.E., and Taveras, E.M. (2016). Risk Factors for Childhood Obesity in the First 1,000 Days: A Systematic Review. Am. J. Prev. Med. 50, 761–779.

World Health Organisation (2001). The optimal duration of exclusive breastfeeding.

World Health Organisation (2011). Childhood overweight and obesity.

World Health Organisation (2014a). Obesity and overweight. Fact Sheet N°311. A.

World Health Organisation (2014b). Global nutrition targets 2025: childhood overweight policy brief (World Health Organization).

World Health Organisation (2016). Report of the Commission on Ending Childhood Obesity (Geneva).

World Health Organisation (2020). Body mass index classifications.

Yan, J., Liu, L., Zhu, Y., Huang, G., and Wang, P.P. (2014). The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health 14, 1267.

Yang, Y., Wang, Z., Mo, M., Muyiduli, X., Wang, S., Li, M., Jiang, S., Wu, Y., Shao, B., Shen, Y., et al. (2018). The association of gestational diabetes mellitus with fetal birth weight. J. Diabetes Complications 32, 635–642.

Ye, J. (2013). Mechanisms of insulin resistance in obesity. Front. Med. 7, 14–24.

Yu, Z., Han, S., Zhu, J., Sun, X., Ji, C., and Guo, X. (2013). Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PloS One 8, e61627.

Zhao, P., Liu, E., Qiao, Y., Katzmarzyk, P.T., Chaput, J.-P., Fogelholm, M., Johnson, W.D., Kuriyan, R., Kurpad, A., Lambert, E.V., et al. (2016). Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study. Diabetologia 59, 2339–2348.

Zheng, M., Lamb, K.E., Grimes, C., Laws, R., Bolton, K., Ong, K.K., and Campbell, K. (2018). Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. Obes. Rev. Off. J. Int. Assoc. Study Obes. 19, 321–332.